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Original Communications

DYSTOCIA IN DIABETES INSIPIDUS

THE RELATION OF PITUITARY OXYTOCIN TO PARTURITION

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THERE is general agreement in the literature that parturition can take place normally in the absence of the hypophysis. For example, Reynolds (1937), in his recent review article on the nature of uterine contractility, stated that no deficiency syndrome involving uterine activity has ever been described for the posterior pituitary lobe. Robson (1936) concluded that "The active changes occurring at parturition and leading to the expulsion of the fetus and placenta may take place in the absence of the pituitary (both anterior and posterior lobes), and in animals with inactive ovaries. Normal parturition may occur at a normal time in pregnancy in cases in which the activity of the pituitary can be excluded." Similarly, Van Dyke (1936), after reviewing the literature, concluded that the mechanism of labor was not under the control of the hypophysis.

During the course of an investigation on the relation of the so-called hypothalamico-hypophyseal system to diabetes insipidus, certain observations have been made which throw doubt on the conclusion that the hypophysis, and more especially its neural lobe, is not involved in parturition. It has been shown that experimental diabetes insipidus can be produced with great regularity in the cat and monkey by placing lesions in the anterior hypothalamus in such a position that they interrupt bilaterally the supraoptic component of the hypothalamico-hypophyseal tract (Fisher, Ingram and Ranson, 1935; Fisher, Ingram,

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M.K.

Hare and Ranson, 1935; Ingram, Fisher and Ranson, 1936). The Horsley-Clarke stereotaxic instrument has been utilized in making the lesions described. For a detailed account of the findings on diabetes insipidus the reader should consult the monograph by Fisher, Ingram and Ranson (1938).

A brief description of the hypothalamico-hypophyseal system will be of assistance at this point. Fig. 1 is a diagrammatic representation of a mid-sagittal section through the hypothalamus and hypophysis of the cat. As can be seen the hypophysis has intimate topographic relations with the hypothalamus. Its neural division may be divided into 3 parts: the expanded portion or (1) *pars nervosa* is connected to the base of the hypothalamus by means of the (2) *infundibular stem* and the (3) *median eminence*. The latter is the rostral continuation of the ventral wall of the infundibular stem which forms a good part of the floor of the third ventricle. The glandular division is likewise composed of 3 parts: (1) the *pars tuberalis* which forms a cuff around the median eminence and the proximal part of the infundibular

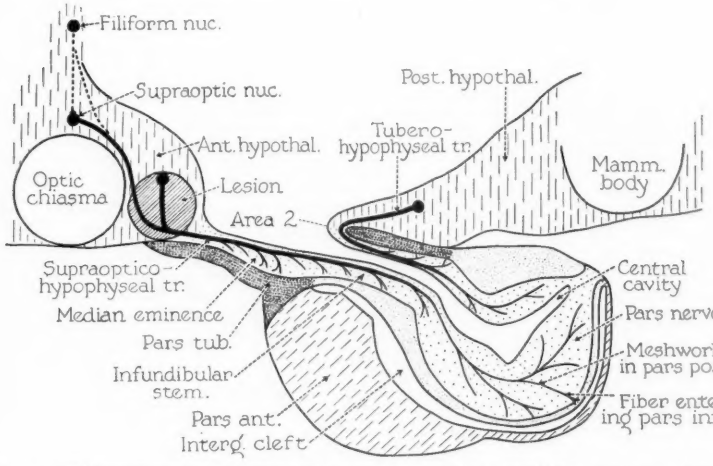

Fig. 1.—Diagrammatic representation of a medial sagittal section through the hypothalamus and hypophysis in the cat. *From Fisher, Ingram, and Ranson:* Diabetes Insipidus and the Neuro-Hormonal Control of Water Balance, Edwards Brothers, Ann Arbor, Mich.)

stem; (2) the *pars intermedia* which completely invests the pars nervosa and is separated by the interglandular cleft from the main component of the glandular division, (3) the *pars anterior*. A heavy bundle of unmyelinated nerve fibers, the hypothalamico-hypophyseal tract, connects the neural division of the hypophysis with the hypothalamus. This tract has 2 components: (1) the supraoptico-hypophyseal tract arises mainly from the supraoptic nucleus and takes the path indicated in Fig. 1 to enter the median eminence, pass through the ventral wall of the infundibular stem and finally to spread out in a dense meshwork in the pars nervosa. (2) The tubero-hypophyseal tract arises from the lateral and caudal peri-infundibular regions and enters the dorsal wall of the infundibular stem. We would emphasize that all 3 parts of the neural division appear to have the same structure, although the median eminence and infundibular stem are somewhat specialized for the conduction of fibers to the pars nervosa.

The obliquely striped circle in Fig. 1 represents the location of a typical lesion designed to produce experimental diabetes insipidus. When such lesions are made the neural division of the hypophysis undergoes a series of striking degenerative changes, a detailed account of which will be found in the references given above. Briefly all 3 parts of the neural division show marked thinning and hypercellularity,

the unmyelinated nerve fibers degenerate and the specialized glial elements (pituicytes) disappear. An example of a degenerated and atrophic neural lobe from a cat with diabetes insipidus is shown in Fig. 3 which should be compared with Fig. 2; the latter represents a transverse section through the hypophysis of a normal cat.

It has been shown that the atrophic neural lobes from cats which develop diabetes insipidus, following interruption of the supraoptico-hypophyseal tracts, are markedly deficient in antidiuretic, pressor and, of great importance for the subject under discussion, oxytocic activity (Fisher and Ingram, 1936; Fisher, Ingram and Ranson, 1938). It has been concluded, therefore, that diabetes insipidus is essentially a deficiency syndrome caused by the failure of the atrophic neural division to secrete the antidiuretic hormone.

Diabetes insipidus has been produced in a large number of cats, 85 in all. Among these were 7 animals in various stages of pregnancy at the time of operation. All of these animals carried their litters to

Fig. 2.—Enlarged photograph of a section through the hypophysis of a normal cat. *A*, pars anterior; *C*, central cavity; *I*, pars intermedia; *IC*, interglandular cleft; *N*, pars nervosa.

term but developed a striking disturbance of the delivery mechanism. Four of them died in the course of a greatly prolonged labor during which they were either totally unable to expel the uterine contents or else succeeded in delivering only a part of their young. Two of these animals have already been discussed briefly in a previous paper (Ingram and Fisher, 1937). Three of the 7 animals managed to survive parturition, but only after a protracted period of labor; 2 of these died within a few weeks after delivery. The implications of these results are of sufficient importance to warrant a more detailed discussion.

It will help to clarify the following summary of results if it is pointed out that after bilateral interruption of the supraoptico-hypophyseal tracts the resulting diabetes insipidus develops in several stages. Immediately following operation a temporary increase in the daily fluid exchange of varying proportions makes its appearance

and usually lasts for four or five days. This has been called the *transient phase* of diabetes insipidus. A period of normal water exchange, which has been designated the *normal interphase* then follows. In the majority of cases a persistent increase in the fluid exchange develops about two weeks postoperatively. This is the *permanent phase* of diabetes insipidus.

SUMMARY OF RESULTS

The permanent phase of the diabetes insipidus in the 7 cats under consideration commenced after latent periods varying from eleven to seventeen days. All the animals but one (D61) had well marked increases in the daily fluid exchange, varying from 3 to 10 times the normal. In one instance (D121) the fluid exchange frequently reached about a liter per day, the most severe case of diabetes insipidus we have seen. In Cat D61 only a mild increase in the fluid exchange was observed. Four of the cats were operated upon when pregnancy was about one-half advanced, two when it was two-thirds advanced and one a few days after impregnation.

Labor started in the different animals at periods varying from the nineteenth to the sixtieth postoperative days. In the cat, term is generally considered to be sixty-three days. Continuous observations were not made on these animals so that the precise duration of labor was not determined. However, the minimum time of labor can be calculated in 6 of them. Of these, 4 died in the midst of greatly protracted labors without delivering all their young. Cat D121 was in labor for about forty-eight hours during which time she delivered 4 kittens; 2 were retained and found in utero at autopsy. Cat NS67 died after a labor which lasted at least 12 hours without succeeding in delivering a single one of her 4 young. In a period of at least fifty-five hours Cat NS68 delivered 2 kittens; at autopsy 2 more were found in utero. The observations on Cat D61 were not complete but it is known that she died during the night after one partly delivered fetus was removed from the birth canal. The remaining 3 cats managed to survive parturition and delivered their full litters but only after prolonged labor. The minimum laboring time in Cat NS69 was twenty-nine hours during which 4 kittens were born. Cat NS40 was in labor about forty-eight hours and delivered 3 kittens. The shortest labor occurred in Cat NS66 and this animal was the only one of the series to survive parturition in good health and for a long period. The calculated minimum time of labor in this case was seven and one-half hours, but without doubt it was actually much longer than this since the animal was already in labor when first observed and since this calculation includes the time only up to 6 P.M. of the thirty-ninth postoperative day. The last-born kitten was delivered some time between 6 P.M. on the thirty-ninth day and 8 A.M. of the fortieth day.

In the cases of Cats D61, D121, NS67, and NS68 there can be no doubt about the disturbance of the delivery mechanism. But Cats NS40, NS66, and NS69 managed to survive parturition and the question arises whether labor lasted longer than normal in these instances. Accurate data on the duration of labor in the normal cat are difficult to find. We have seen one normal cat deliver 3 kittens in a period of less than two hours, and Cat NS35, to be discussed presently, gave birth to 3 kittens in a period of one hour. Dr. Windle informs us that he has recently observed a cat deliver 4 kittens in a two-hour period and another expelled 5 in a space of two and one-half hours. We believe, therefore, that Cat NS66 is the only animal of our series whose delivery time may possibly have been within the normal range, but it is more probable that it was prolonged.

There are several other points worth noting. Cats D121, NS67, NS68, and D61 died in the midst of labor. The cause of death was not determined but exhaustion and uterine sepsis probably played a role. All the kittens delivered were full term except for 2 mummified fetuses found in the uterus of Cat NS67. The 2 unborn kittens found in the upper ends of the uterine horns of Cat D121 were straightened to full length and firmly compressed. A similar stretched fetus was found in the

uterus of Cat NS67 and one in Cat NS68; in addition these last two fetuses had macerated skulls. These observations suggest that violent, perhaps uncoordinated uterine contractions had taken place. Five of the 6 cats on which we have observations showed good development of the mammary glands and lactation. Cat NS69 nursed her young for several days, but lactation stopped when the animal began to decline. Cat NS66 cared for and nursed her young for three weeks, and Cat NS40 for nine days.

Of the 3 cats which survived parturition, 2 (NS40 and NS69) gradually declined and were killed on the ninth and eighteenth post-partum days, respectively. Cat NS66 was the only one of the animals which remained in good health for a long period after parturition, and it was in this case that the duration of labor was the shortest.

A few observations are available which indicate that lesions in the hypothalamus, which do not cause diabetes insipidus, also do not interfere with parturition. Two cats were operated upon for diabetes insipidus but failed to develop it. Cat NS35 delivered 3 kittens within the space of an hour on the thirty-fourth postoperative day. She remained in good health and nursed her young. About two weeks post

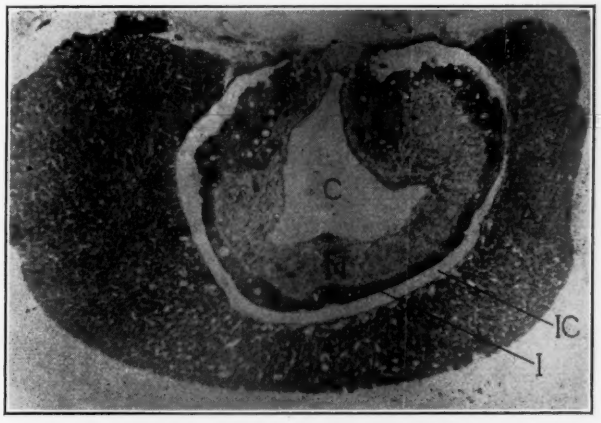

Fig. 3.—Enlarged photograph of a section through the hypophysis of a cat with diabetes insipidus, showing atrophy of the pars nervosa and enlargement of the central cavity. (See legends for Fig. 2 for explanation of lettering.)

partum she came into heat and was mated. Cat NS33 delivered 2 normal full-term kittens on the twenty-first postoperative day. They were born some time between 6 P.M. of one day and 9 A.M. of the next, but the exact duration of labor was not ascertained. The mother nursed the kittens. About a month post-partum she came into heat and was bred. In these 2 cases there was probably partial destruction of the supraoptico-hypophyseal system. Another animal with moderate destruction of the supraoptico-hypophyseal system insufficient to cause diabetes insipidus delivered 3 kittens, which she nursed until they were weaned. A fourth animal with hypothalamic lesions, the location of which was not checked, was bred and delivered 5 kittens which she nursed until weaned. The exact duration of labor in these last 2 cases was not determined, but we know that it was not unduly prolonged.

The hypothalamico-hypophyseal region of Cats D61, D121, and NS67 has been examined in serial sections. In all 3 of these cases the lesions were found in a position to interrupt the supraoptico-hypophyseal tracts. For a detailed description of the lesions and the accompanying degenerative changes in the hypothalamico-hypophyseal system found in animals with diabetes insipidus, the reader is referred to the monograph by Fisher, Ingram and Ranson (1938). A transverse section through the markedly atrophic pars nervosa of Cat D121 is shown in Fig. 3.

DISCUSSION

The obvious explanation for the disturbance of the delivery mechanism in these animals is that they have a deficiency in the amount of pituitary oxytocic hormone. It has been shown that the atrophic neural lobes of cats with diabetes insipidus show little or no oxytocic activity and all of these 7 animals had this disorder (Fisher and Ingram, 1936; Fisher, Ingram and Ranson, 1938). Thus, it was found that 3 normal hypophyses contained 2.5, 3.5, and 2.2 oxytocic units, respectively, while 4 atrophic glands had in each instance less than 0.25 units. Further, the atrophic glands of Cats NS67, NS68, and NS69 have been assayed for their antidiuretic activity. The gland of Cat NS68 was entirely inactive while NS67 and NS69 contained 0.06 and 0.04 antidiuretic units, respectively. Without doubt these glands would have shown a deficiency in oxytocic activity had they been tested.

The degeneration of the hypothalamico-hypophyseal system in these cats and the consequent diminution in the hormone content of the neural division seem to be the only pathology present which could account for the disturbance in parturition. The pars anterior has been found to be normal, or at most only slightly subnormal, in function in animals with diabetes insipidus. This is shown by the integrity of the gonads, thyroids and adrenals in the great majority of instances, by the continuation of growth in young animals and, as we believe, by the development of the permanent phase of the diabetes insipidus itself. The fact that at least 5 of the pregnant cats lactated is further evidence for the presence of pars anterior function (Nelson, 1936).

Although gross atrophy of the ovaries does not appear to develop in diabetic cats, it is possible that there is some abnormality of ovarian function in these animals. We have never observed any of them to come into heat so that pregnancy has never occurred after the diabetes became established. It is doubtful, however, whether a possible disturbance of ovarian function could be related to the abnormal parturition which has been described. Robson (1936) states that parturition can take place in the presence of inactive ovaries and it is well known that pregnancy will continue in women after oophorectomy, and delivery will be perfectly normal.

We hesitate to state positively that the disturbance in parturition which we have observed represents an oxytocic deficiency symptom because our series of animals was not large and our observations conflict with those of previous investigators. It will be well, however, to briefly review the literature on the relation of the hypophysis to parturition to ascertain on just what evidence the oxytocic hormone has so generally been rejected as a factor influencing the mechanism of delivery. It is our opinion that the results so far recorded in the literature do not warrant such rejection, that they have been interpreted uncritically and many of the experiments have been inadequately controlled. The whole problem requires further experimentation and should be thrown open for reconsideration. It may well turn out that the oxytocic hormone of the neural division, like the anti-

diuretic hormone, has an actual physiologic function and is something more than an interesting pharmacologic artefact; it is, after all, one of the most potent uterus-contracting substances known.

In attacking this problem experimentally the natural thing to do is to remove the neural division of the hypophysis or bring about its degeneration, determining subsequently the effect upon parturition. Actually this procedure has been followed by previous investigators in only a few instances. In most cases the entire hypophysis has been extirpated. There are 2 other factors which should be taken into consideration in evaluating the evidence on this subject. First, an adequate histologic examination of the hypophyseal region must be an absolute prerequisite to the acceptance of any conclusions drawn from extirpation experiments. For it has been our experience that the presence of remnants of the median eminence and infundibular stem usually prevents the development of the permanent phase of diabetes insipidus and may likewise permit of normal parturition. It has been emphasized that the 3 parts of the neural division of the hypophysis, namely, the median eminence, infundibular stem and pars nervosa, represent an anatomic unit and it appears probable that they act also as a functional unit. Second, some statement as to the duration of labor should be demanded.

On the basis of one or another of the above criticisms the work of the following investigators must be accepted with some caution. Allan and Wiles (1932), McPhail (1935a), Pencharz and Lyons (1933-1934), Selye, Collip and Thomson (1933-1934), McPhail (1935b) and Firor (1933).

Smith (1932) is the only investigator who has specifically studied the effect of isolated posterior lobe removal on parturition, and his work has been widely quoted as proving the nonessentiality of the posterior lobe in parturition. It should be pointed out that Smith expressly stated that the infundibular stem and pars tuberalis were left intact in his small series of 6 rats and, therefore, the extirpation of the neural division cannot be said to have been complete. Further, no statement was given as to the duration of labor in comparison with normal rats.

Keller and Hamilton (1937) reported the case of a dog with diabetes insipidus following section of the infundibular stem which bred and delivered a litter of 3 pups at term, but no data were given as to the duration of labor.

In spite of statements to the contrary, disturbances of the mechanism of parturition following hypophysectomy have been observed by other investigators which appear to resemble very closely those which we have observed. The most extensive investigation is that of Pencharz and Long (1933). In a series of 28 rats hypophysectomized from the eleventh to the twentieth days of pregnancy a marked derangement of the birth mechanism was observed. This disturbance took one of two forms: either the mother died at the end of a prolonged period of gestation (three or four days past term) without delivering her young or the birth of dead and living young occurred after a similarly prolonged period of pregnancy. As in our cats, macerated and greatly elongated fetuses were found in utero.

Pencharz and Long believed that the derangement of the birth mechanism which they observed was due to the removal of the pars anterior and not to the absence of the neural division. In only a few instances did they make serial sections of the brain base and the pituitary, the completeness of the operation at autopsy being checked in most cases by examining the hypophyseal region under a dissecting binocular. They concluded that the disturbance of parturition appeared only when the pars anterior was reduced to approximately one-fourth of the entire gland. In the absence of a microscopic examination it may reasonably be maintained that in those cases where larger remnants of the pars anterior were left intact greater portions of the neural division likewise escaped extirpation, and that it was this rather than the presence of more pars anterior tissue which prevented the development of the disturbance of parturition.

The results of Pencharz and Long have been duplicated by Selye, Collip and Thomson (1932-1933) and by Bergman (1934a, b), both working on the rat. In neither case was there a microscopic report.

We are not here concerned with the complex matter of the mechanism of labor except to point out that the demonstration that pituitary oxytocin plays a role in those changes which lead to the expulsion of the fetuses at parturition does not conflict with the prevailing theories of the mechanism of labor. In fact, such a demonstration would lend support to these theories and supply one important missing link. Marrian and Newton (1935) have pointed out that there is a considerable body of opinion in favor of the view that labor is determined by a critical concentration of two or more hormones being simultaneously achieved. For instance, that under the influence of increasing amounts of estrin the uterus becomes more and more sensitive to oxytocin with the advance of pregnancy until the threshold concentration is reached. One major stumbling block to the estrin-oxytocin synergism theory is the fact that the hypophyseal extirpation experiments reviewed above have been generally interpreted as excluding oxytocin from the process of parturition. For this reason Marrian and Newton suggest that there may be an extrahypophyseal source of oxytocin, and Bell and Robson (1937) have considered the possibility that the fetal pituitary may supply oxytocic hormone which passes into the maternal circulation and influences the process of parturition.

Finally, we would like to refer to a recent article by Newton (1937) on the insensitivity of the cervix uteri to oxytocin. This author points out that if evidence is ever brought forward proving that the oxytocic principle is involved in parturition, "it must take account of the fact that mere contraction of the uterus is too primitive a process to be dignified by the name of parturition: it is impossible, for instance, to visualize the delivery of the fetuses, five in each horn of the uterus, without some coordinating mechanism. It is not necessary to endow the oxytocic principle itself with any coordinating function, for the type of muscular activity might be determined by some other factor, the oxytocic principle serving merely to potentiate the contractions. It is, on the other hand, necessary to postulate that this should not cause incoordinated movements." The most severe type

of incoordination, according to Newton, would be a simultaneous contraction of the cervix and cornua of the uterus, for this would prevent the expulsion of the fetuses. It appears, however, that such simultaneous contraction does not take place, for Newton was able to demonstrate that in the rat and guinea pig, in any phase of sexual activity, the cervix uteri does not react *in vitro* to large doses of Pitocin. The conclusion was drawn that the oxytocic principle still cannot be excluded from the factors responsible for parturition.

SUMMARY

Observations have been presented on 7 cats in which experimental diabetes insipidus was produced during various stages of pregnancy by making appropriate lesions in the hypothalamus. It was shown that these animals developed striking disturbances of the mechanism of parturition during which they were totally or partially unable to deliver their young or else succeeded in doing this only after a greatly prolonged labor which lasted in some cases over two days. Four of the cats died in the midst of labor; 2 survived for some days but finally succumbed; only one remained alive and in good condition.

These findings were discussed in relation to the theory that the disturbance noted was due to a deficiency in pituitary oxytocic hormone consequent upon interruption of the hypothalamico-hypophyseal tract. A critical analysis of the literature covering the effect of hypophyseal ablation on the delivery mechanism was presented. It was concluded that the work so far reported does not warrant the rejection of pituitary oxytocin as a factor involved in normal parturition, and the suggestion was made that the problem should be thrown open for further investigation.

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THE HISTOLOGIC CORRELATIONSHIP OF ENDOMETRIAL AND CERVICAL BIOPSIES

With Comments on the Etiology of Endocervicitis

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RECENT advances in gynecologic endocrinology, notably the isolation of the two ovarian hormones, and the experimental proof of their respective physiologic effects on the structure of the mucous membranes, gave a new impetus to research work on the endometrium. Experimental observations on animals and castrated women furnish conclusive evidence that estrogen, the hormone of the growing and ripe follicle causes proliferation in the endometrium, and that its prolonged and continuous action produces glandular hyperplasia in this structure. The corpus luteum hormone, progestin, on the other hand, causes certain cytologic changes in the epithelial elements, the manifestation of which is the secretory function.

Since the physiological effects of the actions of both ovarian hormones were clearly defined, attempts have been made to interpret histologic findings in the endometrium on the basis of the recent explanations of hormonal activity. It seems logical that if the specific hormonal effect on the mucous membranes is known, a careful interpretation of the histologic picture may disclose the status of hormonal balance in the ovaries. There being no rest period in ovarian function, the hormone balance is a constantly changing process, and consequently the mucous membranes of the genital tract must undergo a continuous structural change. It is evident that the histologic study of a single specimen, obtained from the mucous membranes at any one phase of the menstrual cycle, cannot be utilized for a reconstruction of the ovarian mechanism. To judge an individual's endocrine make-up on the basis of the ever-changing balance of the ovarian hormones, it is necessary that several biopsies be obtained during one intermenstrual period. A comparative study of such specimens may reveal the true picture of the ovarian mechanism, which seems to be a highly individual and intricate process.

Various ingenious methods were devised to obtain endometrial fragments for microscopic examination, but none of these procedures makes an intensive and reliable periodic investigation of the menstrual cycle feasible. The amount of tissue obtained by suction or punch biopsies is often insufficient for a conclusive diagnosis of the menstrual phase in the endometrium. It must be remembered that the histologic cycle of the endometrium is not a uniform and synchronous tissue change. Rock and Bartlett[1] rightly emphasize the importance of getting the endometrial biopsies from high on the anterior or posterior walls of the uterus, be-

cause only there are the cytologic changes complete. It is obvious that a comparative study of subsequent biopsies taken from different levels of the lining membranes will lead to misinterpretations. The selection of proper areas within the uterine cavity is difficult, and to obtain four or five subsequent specimens in one intermenstrual period from the same level of a surface, not yet denuded of endometrium, is well nigh impossible. Furthermore, clinical observations prove that repeated intrauterine manipulations have a disturbing effect on the normal menstrual cycle. Previously normally menstruating women are prone to show irregularities of their menstrual dates after such procedures. These temporary disturbances of the normal hormonal set-up, the cause of which is unknown, may also result in misinterpretations. In addition to these fundamental disadvantages of periodic endometrial biopsy methods, it also remains questionable whether a sufficiently large number of women can be induced to submit to weekly intrauterine manipulations for diagnostic purposes. It is a painful procedure which cannot always be carried out without some form of anesthesia, and it is not unlikely that its universal application may eventually result in serious aftereffects in some cases, as a result of traumatization or infectious processes.

A tissue index other than the endometrium is available in the human being; a histologic structure, which is easily accessible, which permits a periodic study by simple and safe methods, and which furnishes reliable evidence of the ovarian activity. The results of my investigations[2, 3] of the cervical mucosa indicate that this histologic structure may be the test object which fulfills all the requirements. In my previous publications[2, 3] I described the method used for obtaining cervical tissue specimens for histologic study, and reported my observations on the cyclic changes in this tissue. In my hands the cervical biopsy method proved to be safe, simple, and reliable. It is essential that a 3 to 4 mm. wide strip should be removed from the entire length of the cervical canal. The circular surface of the endocervix offers a large enough area for taking four or five such specimens at weekly intervals. The re-epithelization of the denuded surface progresses rapidly, and three weeks after the removal of the last specimen a perfectly normal looking cervix can be visualized through the speculum. In my cases no inflammatory reaction followed excision, normal menstruation was not disturbed, and all my patients menstruated at the expected time and continued to have normal periods thereafter.

The demonstration of a histologic cycle in the cervical mucosa, which I reported in a previous paper, did not conclusively prove its interdependence with the ovarian cycle. It therefore became my purpose in the present study to investigate the correlationship between changes found in the cervical mucosa and the known effects of ovarian hormone activity. A direct method of studying the ovarian cycle in the human being not being practicable, I selected an indirect way, by undertaking a comparative histologic study of the endometrium and cervical mucosa, both specimens being removed from the same individual at the same time. The histologic effects of the ovarian hormones on the endometrium are so well established that the cytologic changes in this structure constitute

a reliable basis for the determination of the cervical mucosa's corresponding participation in the ovarian cycle.

All together, 44 women were studied in this series. Since it was necessary to obtain liberal amounts of endometrial tissue for the desired purposes, it seemed wise to secure them by means of dilatation and curettage under gas anesthesia. Immediately after removing the endometrial specimen, an approximately 4 mm. wide strip was excised from the entire length of the cervical canal.

All of the patients had normal menstrual histories and normal pelvic organs. Their ages varied from 26 to 43 years. Only 35 of the 44 could be utilized for the purposes of this study, because, notwithstanding the curettage, the endometrial tissue obtained proved insufficient to justify a positive diagnosis. It seems that normal endometria cannot always be readily obtained, even by curettage, particularly in the early proliferative phase of the cycle. On the other hand, no such difficulty is experienced with the cervical biopsy method, as it is always easy to remove the desired amount of tissue by means of the cutting current.

In the 35 cases, in which both specimens could be adequately studied, the entire span of the intermenstrual period was represented. On two days, the fourteenth and sixteenth after the beginning of the previous menstruation, only one case each came under observation; on all of the other days, two or more cases were available for investigation.

The histologic features of the endometrial cycle on the basis of recent endocrine knowledge have been clearly elucidated by various authors (Burch,[4] Campbell and others,[5] Herrell and Broders,[6] and Rock and Bartlett[1]) but the arbitrary division of the intermenstrual period into different phases is still under discussion. In accordance with the ovarian hormone action, the influence of which governs the histologic changes, the intermenstrual period may be divided into two phases: (1) estrin phase and (2) estrin, corpus luteum phase. Due to the progressive changes in both of these phases a subdivision into, (a) early proliferative, (b) late proliferative, (c) early secretory, and (d) late secretory phases is practical from a histologic standpoint. Since the hormonal action is continuous and progressive, a constant change takes place in the mucous membranes, which is neither uniform nor synchronous, and therefore time limits for the different phases are necessarily theoretical and not always substantiated by microscopic observations.

The endometrial changes in the estrin phase are characterized by frequent mitoses, the glandular elments increasing in number and size. The epithelial cells, which at first are distinctly cuboidal or low columnar become gradually higher, and at the peak of estrin production become ill-defined, bulging, crowded, and irregular. The nuclei of the cells also undergo a change. They are deeply stained, oval-shaped, and basally arranged in the early proliferative stage, and later become elongated, spindle-shaped, pale, and centrally migrating bodies. The stroma changes from a dense, fibrous tissue with collapsed blood vessels into a highly edematous, cellular, engorged structure. The corpus luteum hormone has a qualitative influence on the cells, which manifests itself in secretory activity.

In a previous paper, I demonstrated that the cervical mucosa undergoes much the same change as the endometrium, and this statement is corroborated by the results of the present investigation.

I classified the specimens in the following four menstrual groups: (1) early proliferative, (2) late proliferative, (3) early secretory, and (4) late secretory. The comparative study of the endometrial and cervical biopsies revealed a synchronous hormonal action in both structures, but the histologic picture failed to correspond with the known menstrual dates in all cases. In three of them a discrepancy was found between the histologic findings and the clinical history of menstruation. One of these cases is worthy of special mention. The patient was 26 years old, had always menstruated regularly, and had normal pelvic organs. Endometrial and cervical specimens were obtained on the twenty-third day after the first day of her last menstruation. The microscopic picture of the endometrium was characteristic of beginning late proliferation, but the histology of the cervical specimen corresponded exactly with the clinical menstrual date. So in this instance the histologic study of the cervical mucosa gave a more accurate diagnosis of the cyclic phase than did the endometrium. A possible explanation of this discrepancy between endometrial and cervical findings may be that the endometrial specimen was secured from an area of the uterine lining which was not representative of the cyclic phase, and in which the cytologic transformation was not complete. This observation seems to indicate that endometrial biopsies, even if obtained by curettage, cannot always be relied upon from an endocrinologic diagnostic standpoint.

The appended brief histories, with histologic findings and photomicrographs illustrating the specimens, are typical examples of each menstrual phase.

CASE 1.—A 37-year-old woman, married twelve years. Had two children: 8 and 5 years old. Normal deliveries. Had one miscarriage four months ago. Menstrual history normal, usually of four days' duration; last period: May 1 to 5. Endometrial and cervical biopsies were taken on May 7.

Study of the endometrium revealed the following: The glands were stretched with small lumina and were lined by a single layer of low columnar epithelium. The individual cells were well defined and showed relatively little cytoplasm. The nuclei were oval and had a basal arrangement. There were a conspicuous number of typical mitoses. The interglandular stroma was dense, the cells showing deep staining nuclei with little cytoplasm. There were scattered lymphocytes and a few leucocytes in the stroma.

The cervical biopsy specimen showed the following histologic picture: the surface was covered by moderately high columnar epithelium with deeply stained, oval-shaped nuclei, showing a basal arrangement. The individual epithelial cells were sharply defined and formed a continuous layer on the surface. The glands were scanty with narrow lumina and devoid of secretion. The lining consisted of a single layer of low columnar epithelium, the nuclei were deeply stained, oval shaped, and situated near the basal membrane. The stroma was dense, fibrous tissue, the cells having small deeply stained nuclei with inconspicuous cytoplasm. The vessels were collapsed.

Fig. 1 was a high power photomicrograph of the endometrial, Fig. 2 of the cervical biopsy of this case.

CASE 2.—A 39-year-old woman, married nineteen years. Had five children, the last one, two and a half years ago. She had had several miscarriages, the last

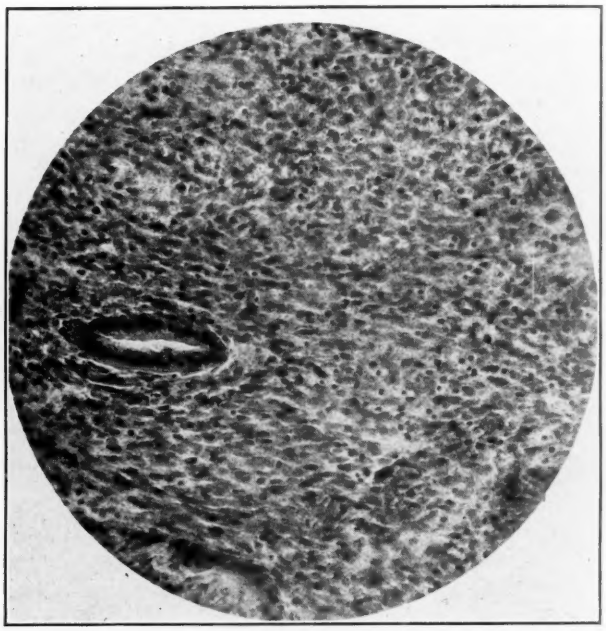

Fig. 1.—Endometrium of the early proliferative phase.

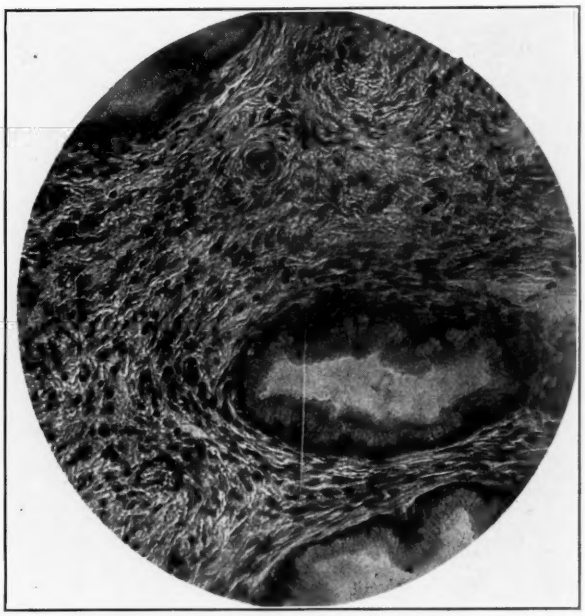

Fig. 2.—Endocervix of the early proliferative phase.

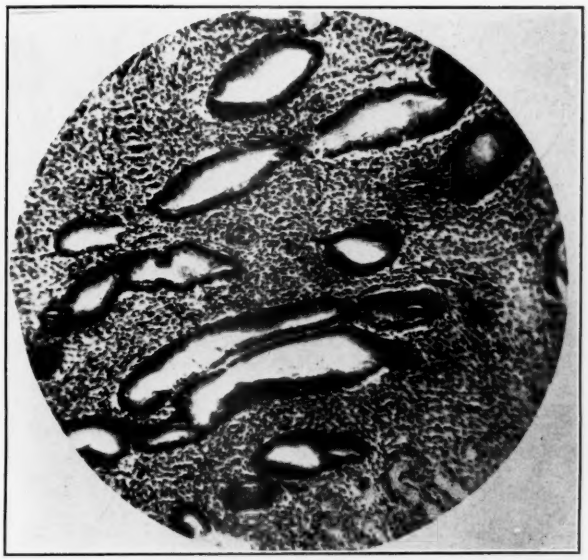

Fig. 3.—Endometrium of the late proliferative phase.

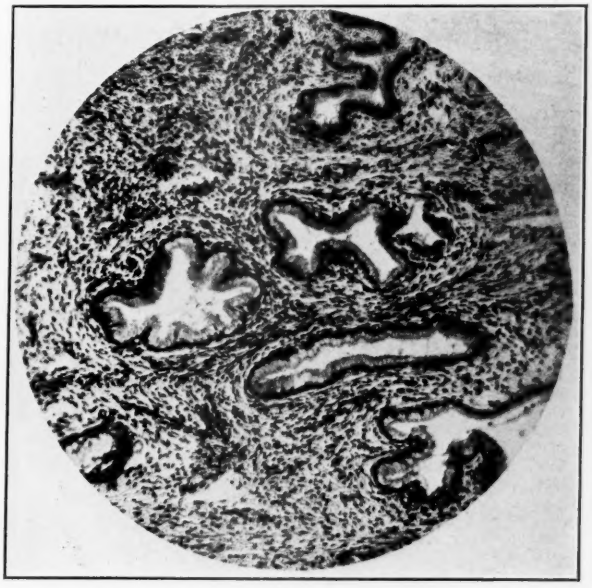

Fig. 4.—Endocervix of the late proliferative phase.

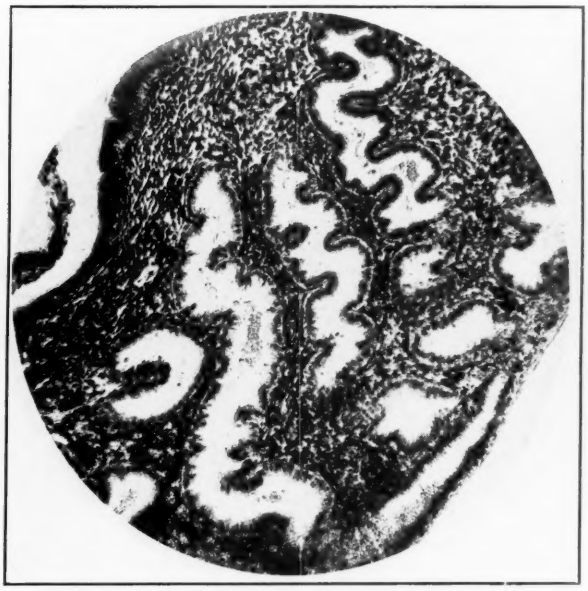

Fig. 5.—Endometrium of the early secretory phase.

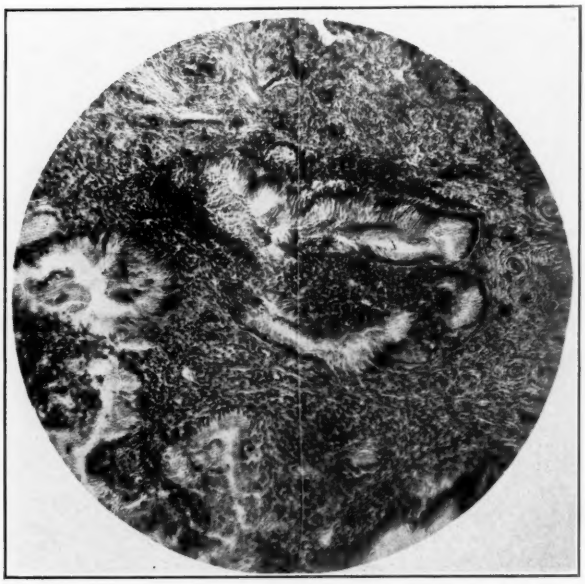

Fig. 6.—Endocervix of the early secretory phase.

Fig. 7.—Endometrium of the late secretory phase.

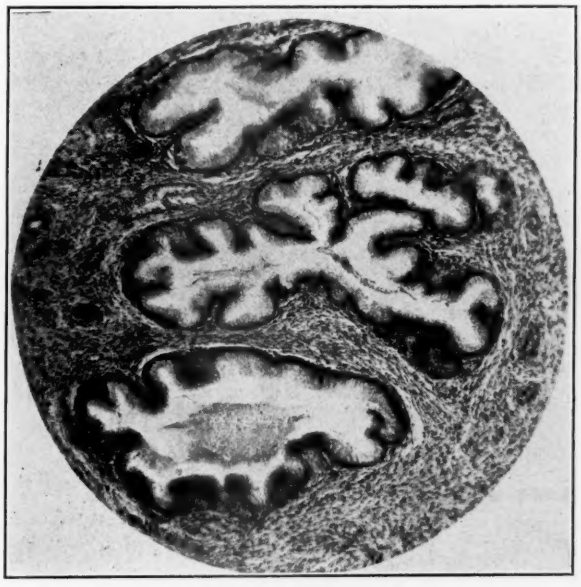

Fig. 8.—Endocervix of the late secretory phase.

one five years ago. She menstruated every twenty-eight to thirty days, three days' duration, of moderate amount. Last period: January 29 to 31. The biopsies were taken on February 9.

Endometrial findings: The glands were slightly wavy and lined by a single layer of high columnar epithelium. The nuclei were somewhat elongated and close to the basal membrane. There were occasional mitotic figures. The interglandular stroma had small nuclei with little cytoplasm. There were areas, however, in which the stroma cells were large with pale stained nuclei. Scattered lymphocytes could be seen.

The cervical tissue: The surface was covered by a continuous layer of high columnar epithelium with oval shaped nuclei, which were deeply stained and which lay near the basal membrane. The glands were few, widely separated, and their epithelium was similar in every respect to the covering epithelium. The individual cells were well defined. The interglandular stroma was moderately cellular.

Fig. 3 demonstrates the endometrial, Fig. 4 the cervical specimen in this case.

CASE 3.—23-year-old woman, married six years. Had had one child six years ago. Menstruation occurred every twenty-eight days, four to five days' duration, moderate amount. Last period: April 20. Biopsies were taken on May 13.

Endometrial findings: The glands were tortuous and moderately dilated. The lining epithelium was high columnar. The nuclei were swollen and had a basal arrangement. The cytoplasm showed vacuolization in many places. The cells of the stroma were slightly swollen and near the surface they were separated by edema. The arterioles were prominent.

Cervical findings: The glands were numerous and presented a great variety of shape and form. Numerous projections into the lumen were seen. The lining epithelium was high with conspicuous cytoplasm. The nuclei were elongated and migrated to the center of the cell. The stroma was edematous and the vessels were prominent.

Fig. 5 shows the endometrial specimen and Fig. 6 the cervical specimen in this case.

CASE 4.—A 38-year-old woman, married fifteen years. Had had two children, the last one eight years ago. Four miscarriages, the last one five years ago. Menstruation occurred regularly every twenty-eight days, and was of six days' duration. Last period: December 17 to 23. Biopsies were taken on January 12.

Endometrial findings: The glands were markedly dilated and the lining epithelium revealed highly vacuolized columnar cells. The stroma cells were large with large pale nuclei and much cytoplasm. Among the stroma cells there were many lymphocytes. The arterioles were prominent and had thick walls: the capillaries were dilated and filled with erythrocytes.

Cervical findings: Numerous glands which were widely dilated and filled with mucus. The lining epithelium was high columnar; the cells were ill defined and bulged into the lumen. The basal arrangement of the nuclei was indistinct. The stroma revealed increased cellularity and prominent thick-walled arterioles.

Fig. 7 represents the endometrial, Fig. 8 the cervical specimen in this case.

DISCUSSION

A comparative histologic study of endometrial and cervical biopsies, taken from normally menstruating women with apparently normal genital organs, revealed identical and synchronous cyclic changes in both structures. The histologic effects of the ovarian hormones can be demonstrated as clearly in the mucosa of the uterine cervix as in the endometrium. In the study of the histologic cycle in human beings, the periodic cervical biopsy method offers distinct advantages over the endometrial biopsy procedures. These advantages are: (1) it always

is possible to obtain the desired amount of tissue for histologic study; (2) the specimens always comprising the entire length of the endocervix, a comparative study of subsequent biopsies is based on findings of identical structures of the mucous membranes; (3) the site of previous excisions is visible, which makes the selection of intact surfaces possible; (4) the histologic interpretation is facilitated by the fact that a compact piece of tissue is obtained, in which the different structural elements are found side by side, as they actually exist in situ; (5) the periodic cervical biopsy method can be carried out at weekly intervals as an office procedure, without anesthesia; (6) the regularity of menstruation is not affected.

I believe that the use of the cervical mucosa as a test-object will make possible an intensive study of the sex cycle in the human being. Definite knowledge of a histologic cycle in the endocervix is bound to change the interpretations of certain pathologic findings in this particular structure. Inflammatory diseases of the cervix are frequently diagnosed. Such a diagnosis may be based on histologic findings, or more commonly on the presence of clinical symptoms, of which an increased discharge from the cervical canal is regarded as most significant. The etiology of endocervicitis is often obscure, especially in young girls who are still virgins and who have no history of infection.

The histologic features of different types of endocervicitis were reviewed recently by Goodall and Power[7] in a concise manner. Among other things, they stated that: "In the mild form of chronic endocervicitis an increased activity of the surface columnar epithelium is present. The hypersecretive type of cervicitis is characterized by columnar cells having a ragged free margin, expelling huge quantities of mucus. The nucleus moves away from the base of the cell, and it may occasionally ascend as far as the middle, leaving a clear space underneath it. The nucleus does not stain deeply. In the more advanced and intense chronic infections the state of hyperfunction may cause a complete explosion of the secreting cells with or without attempts at repair in the deepest basal membrane. In still other more acute stages, a wholesale blight may affect all the columnar cells, causing them to be cast off in a state of partial disintegration, not only of the surface, but of all the deeper glands. Secretion is not a prominent feature of this stage, rather destruction captures the attention. In hyperplastic types hyperplasia of the glandular linings is the predominant feature. In many instances a heaping up of tissue is observed, in which secretory function is partially or totally lost and cell energy seems to spend itself chiefly in division. The columnar cells lose their columnar mucus-secreting characteristics. The underlying stroma is usually but slightly affected by the infection. In acute interstitial cervicitis diffuse round cell infiltration of the deep tissues is present. Thrombophlebitic changes are frequent and consequent diapedesis or large venous hemorrhages do occur. Cystic disease of the glands usually occurs only in the chronic state."

In the course of my periodic cervical studies, I observed all of these supposedly inflammatory pictures at one or another phase of the histologic cycle and found them to be the characteristic manifestations of this structure's physiologic function. These changes were not of a permanent nature, but were found as different stages in the cyclic transformation of the endocervix. Increased activity of the columnar cells with mucus production and migrations of the nuclei is always observed in the secretory phase of the cycle. Exfoliation of the epithelium on the surface

and in the glands is physiologic shortly before and during menstruation. The heaping up of columnar cells with frequent divisions is present in the proliferative stage. Round cell infiltration and edema of the stroma with occasional diapedesis occur in the late secretory phase.

The present study not only yielded further evidence of the correctness of these observations, but also revealed that all these physiologic changes are not confined to the cervix alone, but are synchronous with similar changes in the endometrium. I therefore feel warranted in suggesting that physiologic phases of the histologic cycle may be erroneously interpreted as inflammatory reactions in the cervical mucosa.

The evaluation of an increased amount of discharge from the cervical canal as an expression of inflammatory involvements also requires revision on the basis of the evidence herein presented. Mucus production is the function of the columnar cells, which cover the surface and line the glands. The amount of mucus produced will depend on the number and intrinsic functional ability of these cells. Both these functions in the cervical mucosa, the proliferation and secretion of the columnar cells, are under hormonal influence. It has been proved by several investigators (Burch,[8] Parkes,[9] Tietze,[10] Kaufman[11]) that estrogen is responsible for the proliferation of the columnar cells in the endometrium. I had the opportunity to experiment on a castrated woman and was able to change an atrophic endocervix into one of the late proliferative type by the administration of large doses of estrin. A detailed report of my observations in this case will be published at some future time. Estrogen increases the size and number of glands in the cervical mucosa as it does in the endometrium. While it is impossible to give exact statistical figures, the study of a large number of specimens of cervical mucosa in the different phases of the intermenstrual period makes it evident that a progressive development of the glandular element takes place in the endocervix. Under normal hormonal activity the absolute number of glands is small in the earliest proliferative phase, and this is followed by a gradual increase in number and size until the peak of estrin production is reached. The increased cervical discharge preceding menstruation, which is a common clinical observation, is physiologic and a concomitant of the ovarian hormone influence on the cervical mucosa.

Glandular hyperplasia with subsequent hypersecretion may be a hormonal phenomenon in the light of our newer knowledge of endocrine function. Our conception of the normal ovarian cycle is a developing and ripening follicle with increasing estrogenic activity followed by ovulation, when the activity of the corpus luteum hormone begins. As the progestin's activity increases, there is a decrease of estrogen activity, and it is believed that the progestin elaborated is able to counteract the effects of estrogen activity. Macroscopic inspection of ovaries in the course of laparotomies, performed on normally menstruating women, indicates that the ovarian mechanism cannot be placed on such a simple

basis. On the surface of even normal ovaries a number of unruptured follicles can often be seen. In one case I withdrew into small syringes the fluids contained in small follicles and had them assayed, with the result that in each of the follicles active estrogenic substance could be detected. Although it seems that in mild cases small follicular cystic areas do not disturb normal menstruation, doubtlessly the cumulative effect of estrogen contained in supernumerous follicles alters the normal hormonal balance in the ovaries and must be reflected in the histologic picture of the mucous membranes. In my cervical specimens I noted a great variation in the absolute number of glands and found them always proportionate to the number of glands in the endometrium. Since we know that estrogenic production regulates the number of glands, a hypersecretion of this hormone is bound to manifest itself by an increased amount of mucus from the cervical canal.

On the basis of my observations it seems likely that in the terminology of endocervicitis we are confronted with problems similar to those pertaining to endometritis after Hitschman and Adler's classic researches. Before the recognition of definite endometrial cyclic changes, certain physiologic transformations of the endometrium were erroneously diagnosed as endometritis. Glandular hyperplasia, which we now know is the result of hormonal hyperfunction, was diagnosed as inflammatory condition.

My research work on the cervical mucosa up to the present time justifies the conclusion that in the study of endocervicitis hormonal factors have to be taken into consideration, and further investigations promise a more scientific understanding of this gynecological problem. The more our research work on the histologic features of the menstrual cycle broadens, the more apparent it is that at present we possess only a meager knowledge of this intricate process. Much more labor in this field is necessary to explain the details of the sexual mechanism. A prerequisite for continued progress in gynecologic endocrinology is an exact knowledge of the sex cycle in normal human beings. It is to be hoped that the utilization of the periodic cervical biopsy method, which I strongly advocate for the study of normal women will be instrumental in developing a better knowledge of the action of the female sex hormones.

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THE CAUSES OF VAGINAL BLEEDING AND THE HISTOLOGY OF THE ENDOMETRIUM AFTER THE MENOPAUSE

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ABNORMAL gynecologic bleeding has a wide variety of causes which differ in their relative importance depending upon the age groups being studied. The change in the causes of this symptom which occurs at the menopause overshadows, however, the change taking place between any two decades. On account of its peculiar significance therefore, bleeding after the menopause is correctly regarded as a special entity by both clinician and pathologist. The chief clinical importance remains the significance of the symptom in the diagnosis of cancer, while pathologic attention is directed at present to the study of late functional reactions in the endometrium and their relationships to neoplastic or other changes in the ovary.

I. GENERAL EFFECT OF INCREASING AGE AND THE MENOPAUSE ON THE CAUSES OF ABNORMAL GYNECOLOGIC BLEEDING

During the fifteen-year period from 1921 to 1935 there were admitted to the Gynecologic Service of the Roosevelt Hospital 12,350 patients of whom 4,362 noted some form of abnormal vaginal bleeding, menorrhagia, metrorrhagia, or a sanguineous discharge. In this study of the causes of vaginal bleeding these cases have been classed according to their diagnosis on discharge from the hospital. When two or more possible causes of bleeding were indicated by this diagnosis, the more probable was accepted according to an occasionally arbitrary but always uniform plan.

The cases were subdivided first according to physiologic age, and second according to decades. Accordingly the decades of 40 to 49 and 50 to 59 each appear twice in Chart 1, a patient being placed in one or the other, depending upon whether she had or had not experienced her menopause. The criterion for regarding a patient as having had her menopause was at least six months of amenorrhea occurring after the age of 40 and preceding the bleeding for which she was treated.

From this preliminary classification (Chart 1), a few points may be emphasized.

1. The relative frequency of functional and unexplained causes of bleeding remains about the same in any decade before the menopause, but decreases thereafter. The peak in total incidence is in the thirties.

2. Bleeding due to some complication of pregnancy, particularly abortion or ectopic pregnancy, has of course its principal incidence in the twenties with a high relative incidence even before that time.

3. Inflammatory disease, usually an endometritis associated with adnexal inflammation, has a similar incidence to that of the complications of pregnancy. Inflammation as an important cause of sanguineous vaginal discharge, however, persists in the form of cervical erosions or senile vaginitis in the menopause.

4. Benign tumors show both their greatest absolute and relative frequency as causes of bleeding shortly before the menopause, due of course to the well-known age incidence of fibroids. There is an abrupt drop in the relative frequency of these tumors after the physiologic change of the menopause.

5. The relation of the menopause to the probability of cancer as the cause of bleeding is spectacularly shown in this chart. The rise in the actual number of cancer cases is less abrupt, beginning in the thirties with cases of cancer of the cervix and maintained after the menopause by the increased frequency of cancer of the corpus.

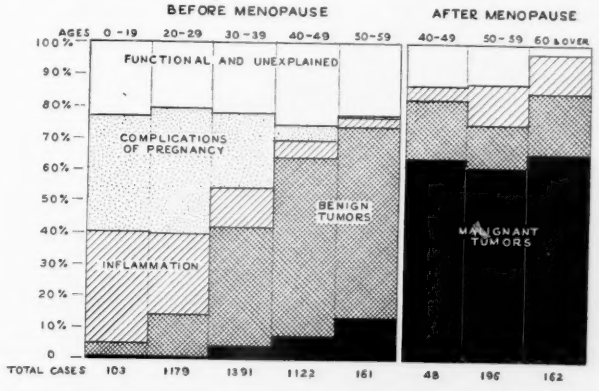

Chart 1.—Relative frequency of causes of gynecologic bleeding in 4,362 cases.

The physiologic change of the menopause is thus far more important in determining the probable cause of bleeding than is any change of a decade in actual years. A woman who is still menstruating, but bleeding abnormally in her fifties, is much less likely to have cancer than is a patient in her forties who experiences a return of bleeding after an early menopause.

II. THE CAUSES OF POSTMENOPAUSAL BLEEDING

The causes of bleeding in the menopause have been classed under four main heads, malignant tumors, inflammation, benign tumors, and functional or unexplained bleeding.

A. *Malignant Disease in the Pelvis.*—Of the 406 patients with postmenopausal bleeding in this series, 259 (63.3 per cent) were associated with some form of cancer. The distribution of these cases is seen in Table I.

Many series of figures have shown that cancer is present in about two-thirds of the patients admitted to hospital services with postmenopausal bleeding. The following figures may be cited: Kantner and Klawans, 68.4 per cent; Fahmy, 43.12 per cent; Geist and Matus, 57.5 per cent; Norris, 52.9 per cent; Zweifel, 87 per cent; Benthin, 42.7 per cent; Brown, 66.8 per cent; Motta, 74.6 per cent; Pemberton and Lockwood, 50.8 per cent; Keene, 61.4 per cent; Ducuing, 92 per cent.

TABLE I. MALIGNANT TUMORS IN CASES OF POSTMENOPAUSAL BLEEDING

	AGES 40-49	AGES 50-59	AGES 60-80	TOTAL
Carcinoma of cervix	22	54	49	125
Carcinoma of corpus	3	53	45	101
Carcinoma of vagina	1	2	6	9
Carcinoma of vulva	3	2	2	7
Carcinoma of ovaries	0	6	2	8
Granulosa cell tumors	0	4	0	4
Myosarcoma of uterus	2	0	3	5
Total	31	121	107	259

These cited statistics are based on hospital patients in whom the incidence of major lesions is of course high. A study of a group of 291 patients with similar symptoms but seen in office practice gave an incidence of malignant disease of only 38.1 per cent (Table II). Even in

TABLE II. PROPORTION OF MALIGNANT CASES IN OFFICE PATIENTS WITH POSTMENOPAUSAL BLEEDING

	NUMBER	PER CENT
Malignant tumors	111	38.1
Benign lesions	180	61.9

the private practice of a gynecologist, however, there is an unusual number of referred cancer cases to continue the emphasis upon cancer as a cause of postmenopausal bleeding. It is probable that of the cases of postmenopausal bleeding which come originally to the family physician as an unsorted group that no more than a fifth have a malignant tumor. This figure is enough to demand care in treatment, but not enough to cause the despair with which the symptom is often greeted.

B. *Benign Inflammatory Lesions.*—This group consists for the most part of the visible inflammatory lesions of the vagina and cervix. Of this group there are 46 cases (Table III).

TABLE III. POSTMENOPAUSAL BLEEDING FROM INFLAMMATORY LESIONS

	AGES 40-49	AGES 50-59	AGES 60-80	TOTAL
Senile vaginitis	0	6	5	11
Prolapse of uterus. Erosion of cervix	0	7	8	15
Erosion of cervix	2	11	5	18
Acute salpingitis	0	0	2	2
Total	2	24	20	46

1. *Senile vaginitis* was the apparent cause of bleeding in 11 patients who were nearly all admitted to the hospital because of doubt as to the diagnosis. This lesion would, of course, be much more common in a group of patients selected from the clinic or office. In two cases of this series, the vaginitis was due to a pessary kept in the vagina over a long period and removable only under anesthesia.

2. *Prolapse of the uterus with erosion of the cervix* was the basis of symptoms in 15 patients all of whom complained of bloody discharge but were operated upon chiefly for the malposition of the uterus. No

lesion of the endometrium was found otherwise to explain the bleeding in 9 of the 10 cases curetted in this group. In one there were signs of a mild endometritis.

3. *Erosion of the cervix,* unsubjected to the trauma that occurs with prolapse, is a more doubtful lesion with which to explain bleeding. Nevertheless in the 15 cases in which a curettage was performed a possible alternative explanation was found in only two.

4. *Salpingitis:* In 2 patients the bleeding was associated with acute inflammatory disease in the pelvis. In neither of these cases was the endometrium available for examination.

5. *Chronic endometritis* has not been classed with the inflammatory lesions because of its doubtful status as a cause of bleeding. It is probably a precipitating cause of the bleeding in cases of submucous fibroids, and possibly in association with erosion and endocervicitis in elderly women. It may exist as a relatively independent lesion as will be discussed below.

C. *Benign Tumors.*—Bleeding occurred in 67 patients in whom benign tumors were present (Table IV). These played a variable role in the production of the symptoms.

TABLE IV. POSTMENOPAUSAL BLEEDING WITH BENIGN TUMORS

	AGES 40-49	AGES 50-59	AGES 60-80	TOTAL
Fibromyomas	7	8	13	28
Fibromyomas and ovarian tumors	1	4	3	8
Ovarian tumors only	0	2	1	3
Cervical polyps	0	9	6	15
Endometrial polyps	1	3	5	9
Urethral caruncles	0	1	3	4
Total	9	27	31	67

1. *Cervical polyps* apparently alone accounted for the bleeding in 15 cases, and 2 more associated with fibroids were possible causes. No doubt many more were treated in the dispensary and offices of the physicians referring patients to the indoor service.

2. *An endometrial polyp* as an uncomplicated lesion was an acceptable cause of bleeding in only nine cases, but such a polyp was found in association with fibroids in five more. This is a relatively low figure, for Benthin found that these growths were responsible for about a quarter of all of his cases of benign postmenopausal bleeding from the body of the uterus.

3. *Fibroids of the uterus* were the most frequent benign tumors noted in this series, a finding contrary to a belief widely held that these tumors cease to cause trouble after the cessation of the menses. The contradiction is only apparent, however, because, as is shown in Table V the bleeding was due in a great majority of the cases not to the tumor itself, but to some special complication. Other investigators such as Shaw have emphasized degeneration of the fibroid as the chief cause of trouble in the menopause, but in this series it is clearly the necrotic and inflammatory changes developing in the submucous pedunculated

TABLE V. COMPLICATIONS AS A FACTOR IN BLEEDING FROM A UTERUS WITH FIBROIDS AFTER THE MENOPAUSE

	TOTAL CASES
Submucous position	12
Ovarian tumors	8
Endometrial polyps	5
Cervical polyps	2
Endometrial hyperplasia	2
Late menstruation	3
Prolapse of uterus	4
(Carcinoma of corpus)	(44)
Total	80

tumor which are chiefly responsible for the bleeding. This list of 36 patients with fibroids includes only benign cases, but in 44 more fibroids were associated with cancer of the body of the uterus. Therefore if all cases of bleeding from the body of the uterus in which fibroids were present are considered, it is found that carcinoma is present in more than half.

4. *Benign ovarian tumors* were the only gross lesions present in three cases, but in eight others, there was bleeding from a fibroid in the uterus,

TABLE VI. POSTMENOPAUSAL BLEEDING WITH OVARIAN TUMORS

	PATH. NO.	AGE	ENDOMETRIUM	OVARY
	Group 1. Bleeding With Benign Ovarian Tumors. Normal Myometrium			
1	S.C. 3871	53	Normal	Pseudomucinous cystadenoma
2	S.C. 3029	52	Atrophic	Papillary serous cystadenoma
3	S.A. 9449	61	No specimen	Pseudomucinous cystadenoma
	Group 2. Bleeding With Benign Ovarian Tumors. Fibromyoma Uteri			
4	S.B. 7019	75	Hyperplasia	Pseudomucinous cystadenoma
5	S.C. 1283	59	Atrophic, cystic	Pseudomucinous cystadenoma
6	S.B. 2593	54	Atrophic	Pseudomucinous cystadenoma
7	S.B. 5109	60	Atrophic, adenomyosis	Pseudomucinous cystadenoma
8	S.C. 199	50	Atrophic, polyp	Papillary serous cystadenoma
9	S.C. 1872	61	Atrophic, polyp	Serous cyst
10	S.C. 4312	48	Atrophic	Serous cyst
11	S.B. 2973	58	No specimen	Parovarian cyst
	Group 3. Bleeding With Granulosa Cell Tumors			
12	S.B. 6383	58	Hyperplasia	Sarcomatous type
13	S.C. 1457	55	Hyperplasia	Diffuse type with luteinization
14	S.C. 9046	59	Hyperplasia	Theca cell type
15	S.C. 1412 S.C. 6240	52	Hyperplasia	Cylindromatous type
	Group 4. Bleeding With Malignant Ovarian Tumors			
16	S.B. 5648	58	Adenocarcinoma	Papillary cystadenocarcinoma
17	S.B. 8060	58	Adenocarcinoma	Papillary cystadenocarcinoma
18	S.C. 5032	60	Adenocarcinoma	Papillary cystadenocarcinoma
19	S.C. 5577	74	Adenocarcinoma	Papillary cystadenocarcinoma
20	S.C. 5782	55	Hyperplasia	Papillary pseudomucinous cystadenocarcinoma
21	S.C. 6569	55	Adenocarcinoma	Papillary cystadenocarcinoma
22	S.D. 2793	52	Atrophy, polyp	Papillary pseudomucinous cystadenocarcinoma
23	S.C. 1130	52	Atrophy	Papillary cystadenocarcinoma

with a benign ovarian tumor also present. To complete the group of cases of bleeding with ovarian new growths there must be also added 8 cases of typical ovarian adenocarcinoma, and four cases of tumors of the granulosa cell type.

The subject of postmenopausal bleeding with ovarian neoplasms has recently received much attention on account of the indication that it gives of a hormone activity of the tumor. Too little emphasis has perhaps been given to the fact that bleeding in the presence of an ovarian tumor is not necessarily a sign that a specific tumor, such as the granulosa cell tumor, is the cause.

Table VI shows that bleeding in association with ovarian tumors may occur under several circumstances.

a. *With an associated carcinoma of the endometrium,* a coincidence occurring in five instances in this series. Whether the tumor is primary in the fundus or in the ovary or whether the tumors are independent coincident growths cannot always be determined.

b. *With an associated hyperplasia of the endometrium.* The relationship of the endometrial lesion to the ovarian tumor is established to a variable degree for the different forms of ovarian neoplasm.

1. The typical granulosa cell tumor is an accepted cause of hyperplasia of the endometrium in the menopause. There were two tumors of this class in the series, one a typical cylindromatous form, the other with signs of luteinization of the granulosa cells.

2. A group of tumors whose structure resembles more closely the stroma of the ovary has a debatable relation to the granulosa cell tumors. Meyer in 1925 reported endometrial hyperplasia in two cases of sarcoma and in one of fibroma of the ovary, but suggested that these might be derived from granulosa cell tumors. More recently there has been an attempt to segregate a new group of tumors, having hormone activity, as theca cell tumors (Loeffler and Priesel, Melnick and Kanter, Geist and Spielman). Novak and Brawner prefer to regard all these tumors as part of the granulosa cell group and as justification cite the theory of a common origin of granulosal, thecal, and stromal tissue from the ovarian mesenchyme (Fischel). According to the conception that one holds, the two tumors of this group may be regarded as granulosa cell tumors, or Case 12 may be considered a sarcoma and Case 14 a fibroma or theca cell tumor.

3. Nonspecific ovarian tumors have occasionally been reported in association with endometrial hyperplasia, but their position as hormone producers has not been accepted. In two patients, one with a pseudomucinous cystadenoma and one with a pseudomucinous cystadenocarcinoma, the endometrium showed numerous glands with a high cylindrical epithelium and large cystic glands. In a third endometrium, also associated with a pseudomucinous cystadenoma, although hyperplasia could not be said to be present, the expected degree of atrophy had not occurred.

CASE 1.—R. N. (History 14659), a 75-year-old married woman, para iv, was admitted for two weeks of vaginal bleeding after not having menstruated for twenty-five years. At operation (Aug. 13, 1926) there were found a cyst, 23 cm. in diameter, of the left ovary, several small fibroids of the uterus, and a nodular area in the right breast. Pathologic examination (S.B. 7019) led to a diagnosis of pseudomucinous cystadenoma of the left ovary, atrophy of the right ovary, fibromyomas of the uterus, chronic cystic mastitis, and hypertrophy of the endometrium. Sections of the endometrium showed many dilated glands of variable size with a well-preserved cuboidal epithelium (Fig. 1).

CASE 2.—(History 19326.) A married woman of 55 years, with two children, was admitted with a history of two recent attacks of vaginal bleeding, beginning fifteen years after her menopause. At operation (Aug. 19, 1931) a 25-cm. cyst of the left

ovary, containing a clear straw-colored fluid, was found and removed. Within the wall was a localized, projecting solid area of evident malignancy. The complete operation consisted in a supravaginal hysterectomy, bilateral salpingo-oophorectomy, and insertion of radium (1800 mg. hours) into the cervical stump. The pathologic report (S.C. 5577) included pseudomucinous cystadenocarcinoma of the left ovary; fibrosis of the right ovary; hyperplasia of the endometrium. Sections of endometri-

Fig. 1.—Cystic hyperplastic glands in a patient of 75 years, with a pseudomucinous cystadenoma (S.B. 7019).

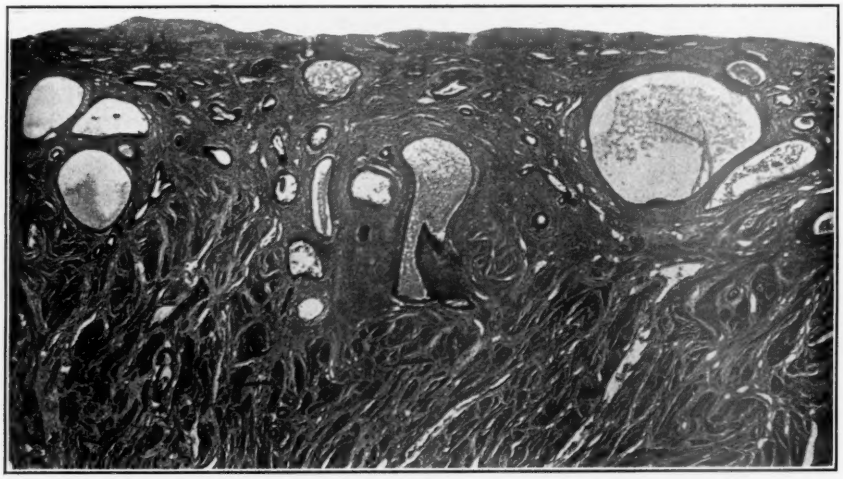

Fig. 2.—Cystic and hyperplastic glands in a patient of 55 years with pseudomucinous cystadenocarcinoma (S.C. 5577).

um (Fig. 2) showed a mucosa of medium thickness, overlying muscle with numerous slender glands and among these, but especially in the basal portions of the endometrium, large dilated cystic structures.

Moulonguet and Doléris, Tietze, and Schiffmann have likewise noted moderate degrees of hyperplasia of the endometrium with several nonspecific types of ovarian tumor. The case which Tietze took for illustration was a mucus-producing adenocarcinoma similar to cases of the present report. Schiffmann has described hyper-

plasia with a Brenner tumor and a pseudomucinous cyst in a woman of 60 years, and an endometrium manifesting at least no evidence of atrophy in a patient of 74 years with a bilateral mucus gland carcinoma of the ovaries.

According to Schiffmann's view, one cannot exclude the possibility of an ovarian effect from these growths, although the hyperplasia is less marked than in the granulosa cell tumors. Tietze, however, expressed the belief that this hyperplasia with the nonspecific ovarian tumors was not an abnormal functional phase but the result of local increased metabolism and blood supply. Whatever may be the cause of the hyperplasia in these cases, the microscopic picture is sufficiently like that produced by the granulosa cell tumors to make it inadvisable to draw ready conclusions as to the character of any palpable ovarian tumor when such endometrial tissue is obtained at curettage.

c. *In the presence of an atrophic endometrium.* In 7 patients bleeding occurred in the presence of an ovarian tumor from an atrophic endometrium. To explain such bleeding it has been customary to assume a pelvic congestion as a result of the tumor with bleeding from the engorged veins in the endometrium. Such distended vessels in the endometrium were evident in several of our specimens. Unrelated causes such as endometritis may be a factor.

D. *Bleeding From Grossly Normal Uteri.*—There remains finally a group of 34 patients in whom no gross inflammatory or neoplastic lesions were demonstrable anywhere in the pelvis (Table VII). For these an essentially endometrial source for the bleeding must be sought.

TABLE VII. BLEEDING FROM GROSSLY NORMAL UTERI

	AGES 40-49	AGES 50-59	AGES 60-80	TOTAL
Prolapse of uterus. Congestion(?)	1	7	1	9
Functional bleeding:				
Interval phase	3	4	0	7
Premenstrual phase	0	1	0	1
Hyperplasia	0	1	2	3
Endometritis in atrophic endometrium	1	6	0	7
No assignable cause:				
Simple atrophy	1	4	1	6
No endometrium	0	1	0	1
Total	6	24	4	34

1. *Vascular Lesions:* The view has been repeatedly expressed that hypertension or chronic passive congestion from a failing heart might be associated with uterine bleeding (Rees, Klotz and Klotz), but instances of systemic cardiac or vascular disease did not occur with unusual frequency in this series of cases. Localized lesions of blood vessels are a more probable source of bleeding. Lahm has emphasized disturbances in circulation but noted also local trauma and constipation as precipitating causes. In nine of the cases of this group, various degrees of uterine prolapse were present as a theoretical source of the venous congestion which might lead to this uterine bleeding.

2. *Endometritis* has been suggested as a cause of postmenopausal bleeding, the inflammation being laid sometimes to cervical stenosis with interruption of proper drainage, sometimes to the loss after the menopause of the protecting plug of cervical mucus. Benthin places inflammations of the endometrium at the head of his list of the benign causes of uterine bleeding in the menopause, and other writers (Breipohl) have given it a prominent position.

The importance of inflammation is difficult to evaluate on the minute fragments of tissue obtained from the senile uterus by curettage. The appearance of many inflammatory cells in tiny fragments of uterine tissue does not determine that the inflammation was the exciting cause of the bleeding, and the reverse may actually

be the case. Histologic evidence of an inflammatory reaction of some sort was present in seven of the 26 cases in which the uterus was grossly normal. Histologic evidence of this endometritis is most definite, however, in fragments of tissue obtained from uteri in which fibroids or polyp are present (Fig. 3).

3. *Late Ovarian Activity:* The possibility of renewed function of the ovary after months or years of apparent inactivity has received little attention until recently. That the endometrium after castration (Kaufmann) or even in extreme old age (Hübscher) could be stimulated to renewed activity by administration of an estrogenic hormone has been proved, and bleeding has been produced artificially. Attempts to reactivate the human ovary, however, have led to contradictory results. Tschertok and Penkow failed to obtain any reaction in ovaries of women injected with pregnancy urine before celiotomy for fibroids, but Westman, who performed similar experiments, claimed to have observed follicle growth and corpus luteum formation.

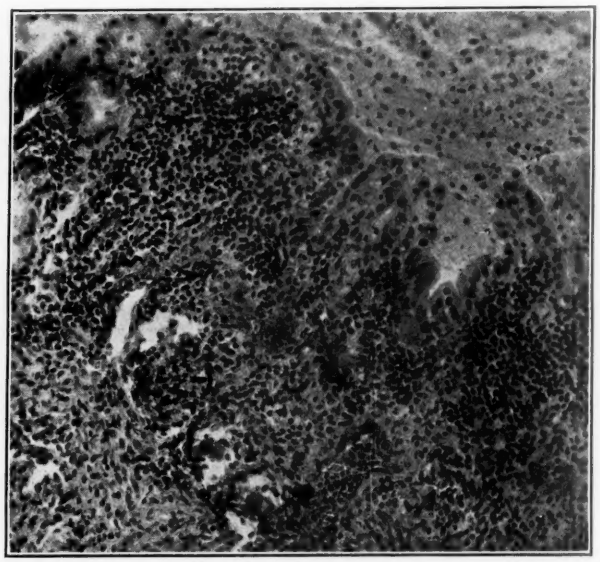

Fig. 3.—Chronic endometritis in a patient of 64 years with an endometrial polyp (S.B. 8949).

In reply to this work of Westman, Waldeyer has recently reported in a series of untreated patients, forty-eight to fifty-four years of age with their menopause from three months to five years behind them, follicle and early corpus luteum development in the ovary and an interval phase of the endometrium. Breipohl in studying the endometria of 130 women over forty-five years of age and at least six months after their supposed menopause, reported 13 with endometria in the proliferative stage and three in a secretory stage. Robert Meyer has also reported a corpus luteum in the menopause.

a. Interval endometrium: In the present series, among the 35 cases with normal pelvic organs there were seven (ages 47, 49, 47, 55, 52, 55, 52) in which little or no atrophy could be noted. Their histology resembled in some respects the interval phase of the normal endometrium, but the glands were less regular and often cystic, and the stroma somewhat dense. In several it was difficult to decide whether to list them as cases of hyperplasia, of which the following case report is an example.

CASE 3.—F. S. (History 14396.) This married childless woman, 55 years of age, was admitted with a history of "metrorrhagia." The uterus was noted as in mid-

position and a little "heavy," the right adnexa prolapsed, the cervix normal. The operation (May 12, 1926), consisting in a dilatation, curettage, and insertion of radium, led to a pathologic diagnosis of hyperplastic endometrium (S.B. 6563). Review of this material showed a surface epithelium of high columnar cells, many round well-formed glands (Fig. 4) whose cells in places showed slight evidence of secretion and finally a few cystic glands, irregular in shape, but still with a well-developed epithelium.

b. Premenstrual endometrium: An early premenstrual phase was found in a patient of 55 years in the group with normal pelvic organs and a fully developed secretory endometrium in a patient of 52 years with a fibroid uterus.

CASE 4.—G. M. (History 18783.) This patient, a 55-year-old married woman with two children was admitted on account of five days of profuse vaginal bleeding after a year's freedom from any regular menstruation. Very slight bleeding had occurred, however, at frequent, perhaps approximately monthly, intervals. The operation (Jan. 28, 1931) consisted in a plastic operation on the vaginal walls and cervix and a curettage with insertion of radium. The pathologic report (S.C. 4581) was "moderate hypertrophy of the endometrium," but re-examination showed in places the rows of irregular gland sections, indicating the tortuous glands of the early premenstrual phase (Fig. 5).

Fig. 4.—Absence of atrophy in endometrial glands of a patient of 55 years (S.B. 6563).

CASE 5.—F. B., History 13503. This 52-year-old patient, the mother of 4 children, had had an apparent menopause at 50, but after skipping several months had, nine months before her admission, begun to bleed at irregular intervals. Examination showed the fundus to be somewhat enlarged and irregular, the cervix and adnexa normal. The operation consisted in a plastic operation on the vaginal walls, a dilatation and curettage and insertion of radium. The pathologic report of the tissue (S.B. 4641) was hyperplasia of the endometrium. Review of the slides has shown a typical premenstrual endometrium with tortuous glands, cells filled with secretion, edema and inflammatory cells in the stroma (Fig. 6).

CASE 6.—In a recent case not belonging to the present series but operated upon at the Bellevue Hospital, a fully developed premenstrual endometrium was encountered in a patient of 55 years. This woman had had bleeding at intervals of several months for two or three years without the establishment of a definite menopause.

Abdominal operation was undertaken because of urinary symptoms and a cystoscopic report of a tumor pressing on the bladder. The uterus was found to be symmetrically enlarged, soft, discolored and a complete hysterectomy with removal of both adnexa was undertaken because of the belief that a carcinoma of the corpus was present. Sections revealed a typical premenstrual endometrium and a corpus luteum in one ovary.

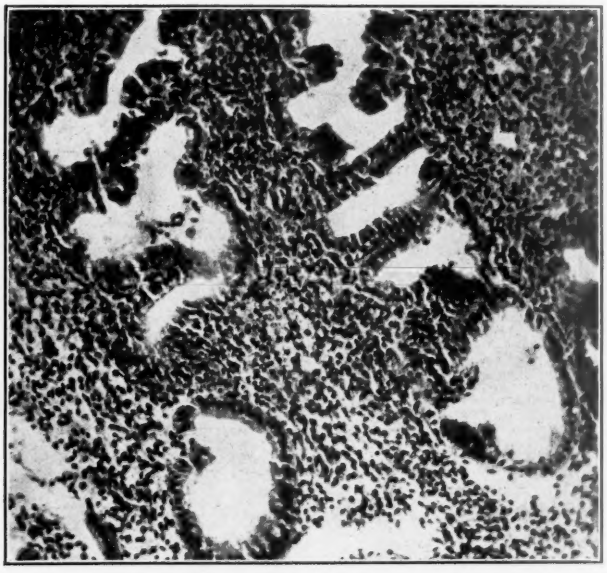

Fig. 5.—Early premenstrual endometrium in a patient of 55 years (S.C. 4581).

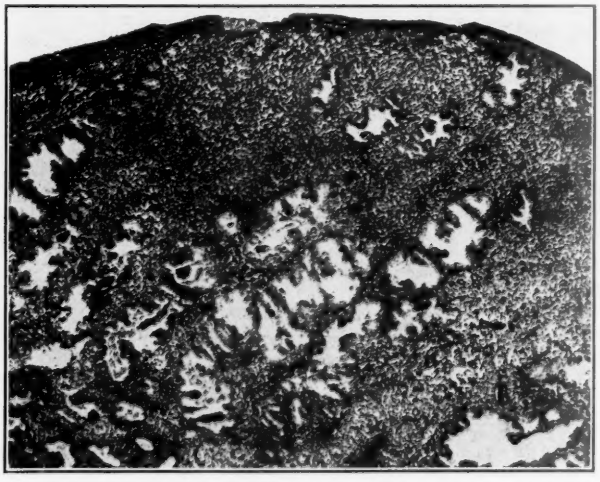

Fig. 6.—Typical premenstrual endometrium in a patient of 52 years (S.B. 4641).

These three cases indicate that up to the age of 55 years and even after intervals of amenorrhea of several months, a normal menstrual period may be the explanation of vaginal bleeding. In none of the cases studied, however, has a typical premenstrual endometrium been found in a woman who, having passed the age of 50, had had more than twelve months of amenorrhea.

c. Hyperplasia of the endometrium. Although endometrial hyperplasia has been regarded as rare after the menopause, cases were reported some time ago by Seitz and by Meyer. In Meyer's case, a woman of 61 years, the failure of three curettages and the success of radiation of the ovaries led to the suggestion that even at this age the ovaries might have an endocrine effect. Endometrial hyperplasia was reported by one of the writers (Taylor) as frequently present near areas of carcinoma of the endometrium, a finding corroborated and amplified by Novak and Yui. Breipohl in a survey of the endometria of the menopause found 15 or 11.53 per cent to be hyperplastic.

Among the 34 patients with otherwise normal pelvic organs in the present series, endometrial hyperplasia was found in three, aged 53, 63, and 63 years, who had had their menopause 13, 13, and 4 years, respectively, before their operation. Among the patients with fibroids uncomplicated by ovarian tumors, there were also 2 cases of hyperplasia, but each of these occurred relatively soon after the menopause. The frequency with which hyperplasia was encountered among these cases of postmenopausal bleeding appears thus to be considerably less than that observed by

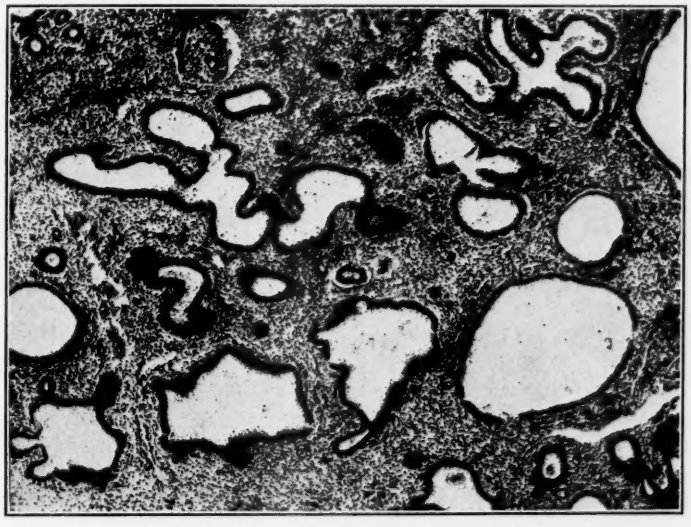

Fig. 7.—Endometrial hyperplasia in a patient of 63 years, ten years after the menopause (S.B. 6979).

Novak and Yui or by Breipohl, but since the cases were selected for different reasons, the material is not wholly comparable. The histories of the three older patients are as follows:

Case 7.—E. A. (History 14613.) This married woman of 63 years, the mother of 7 children, had had a normal menopause at the age of 53, had bled for six days with clots at the age of 61, and now again for six days before admission. Physical examination disclosed no abnormalities. The operation consisted in a curettage and insertion of radium. The endometrium, which could be curetted away in fairly large fragments, was diagnosed as "hyperplastic endometrium (S.B. 6979)." The sections (Fig. 7) of this tissue showed irregular branching as well as cystic glands in a rather dense stroma.

Case 8.—J. H. (History 15403.) This patient, a married woman of 63 years with 2 children, stated that her menopause had not occurred until her fifty-ninth year after which there had been no bleeding until a slight show of blood two weeks before admission. Examination disclosed a somewhat enlarged uterus and otherwise normal pelvic organs. The operation (June 13, 1927) consisted in a dilatation and curettage and the insertion of radium. The pathologic report (S.B. 8566) was

hypertrophy of the endometrium. Review of the sections (Fig. 8) showed a tissue containing many cystic glands of irregular contour and many smaller glands occurring packed together in clusters. The cells of the epithelium were small, cylindrical with the nuclei practically filling the cells. The stroma was dense, cellular infiltrated with blood.

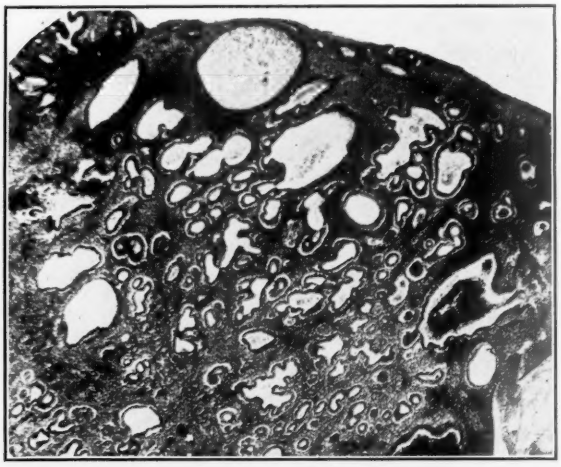

Fig. 8.—Endometrial hyperplasia in a patient of 63 years, four years after the menopause (S.B. 8566).

Fig. 9.—Endometrial hyperplasia in a patient of 58 years, thirteen years after her menopause (S.B. 3025).

CASE 9.—N. O. (History 12650.) This married woman of 58 years, the mother of 9 children, had had a normal menopause at 45, but had again been bleeding slightly for three months before admission. Examination showed the fundus, cervix, and adnexa to be grossly normal. The operation consisted in a curettage and insertion of radium. The pathologic report (S. B. 3025) was chronic endometritis. Review of the sections (Fig. 9) showed numerous glands, mostly quite round but of all sizes. The epithelium in the different glands was strikingly variable, being very

low in some, high columnar in others. The stroma again was cellular, but very dense. This patient continued to bleed and was curetted again on April 25, 1935, but at that time only degenerated tissue was obtained by curettage. No ovarian tumors were ever palpable.

The hyperplasia developing after the menopause is thus in some respects histologically different from that appearing earlier. The stroma tends to be cellular but rather dense. The glands are very irregular in shape, frequently branching, often flattened, and sometimes showing small intraglandular papillae. Occasionally, however, the glands are round and cystlike with a flattened cellular lining. The epithelium of adjacent glands is often strikingly dissimilar, all variations being present from flat to high columnar cells. The process suggests a renewed growth of some glands superimposed upon an atrophy of the old mucosa.

The basis of the late hyperplasia is open to considerable dispute. Two principal views are admissible. First the cause of the hyperplasia may be the ovarian hormone, as is true for the younger cases, but special consideration is necessary to explain its source. It is possible first that small granulosa cell tumors may be present and yet not evident to the examiner. This occurrence has been previously reported,

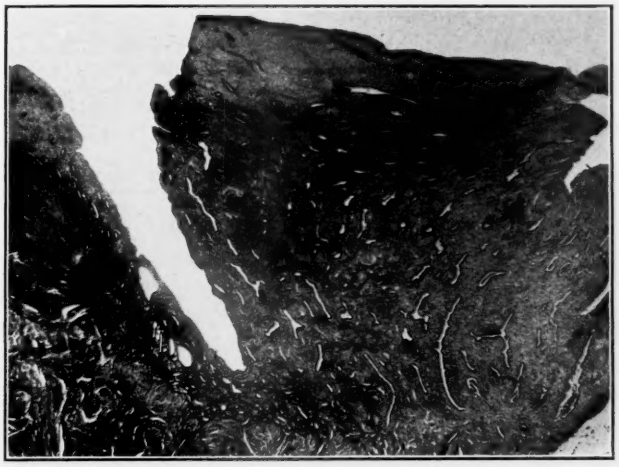

Fig. 10.—Localized hyperplasia or polyp of endometrium (S.D. 2793).

and one of our own cases of granulosa cell tumor was missed at the time of the patient's first curettage for postmenopausal bleeding. Second, a late development of follicles may be responsible, for cystic conditions of the ovary have in fact been reported many years after the menopause. Whether these form the estrogenic hormone in amounts sufficient to influence the endometrium is not known. Considerable quantities of estrogenic hormone do continue to be excreted in the urine many years after the menopause and even in castrates (Frank, Goldberger and Salmon). The latter indicates an extraovarian source for this substance which again may be a basis for endometrial proliferation. It is finally a possibility that the histologic change produced by the ovarian function at or before the menopause may persist for years to give the impression of a late ovarian activity.

The second major conception is that this hyperplasia is a process of a less physiologic and more neoplastic character due to other types of stimuli, perhaps purely local. In material obtained by curettage it is in fact often difficult to determine whether one is dealing with fragments of small polyps or a strip of endometrium. But besides the confusion due to technical deficiencies there are probably more or less transitional forms between purely localized polyps and diffuse hyperplasia. Fig. 10 shows a flat, plateau-like structure arising a little above the remaining endometrium, which is apparently a localized process but which has a wide

TABLE VIII. THE ENDOMETRIAL FINDINGS IN THE MENOPAUSE*

CLASSIFICATION OF CAUSE OF BLEEDING		AGE 40-49							AGES 50-59							AGES 60-80						
		ATROPHY	INTERVAL PHASE	PREMENSTRUAL PHASE	HYPERPLASIA	ENDOMETRIAL POLYP	CARCINOMA	NO ENDOMETRIUM	ATROPHY	INTERVAL PHASE	PREMENSTRUAL PHASE	HYPERPLASIA	ENDOMETRIAL POLYP	CARCINOMA	NO ENDOMETRIUM	ATROPHY	INTERVAL PHASE	PREMENSTRUAL PHASE	HYPERPLASIA	ENDOMETRIAL POLYP	CARCINOMA	NO ENDOMETRIUM
Senile vaginitis	11	0						0	5						1	3						2
Prolapse. Cervical erosion	15	0						0	5						2	5						3
Cervical erosion	18	1	1						9						2	5						
Salpingitis	2																					2
Uterine fibroids	28	1	2		2			2	4		1		(2)		3	6				(1)		7
Fibroids and ovarian tumors	8	1							3				(1)		1	2			1	(1)		
Benign ovarian tumors	3								1	1												1
Cervical polyps	15								3						6							6
Endometrial polyps	9					(1)		1					(3)		3					(5)		5
Urethral caruncles	4														1	2						1
Carcinoma of ovary	8								2			1	(1)	(3)	3						(2)	2
Granulosa cell tumors	4											4										
Simple prolapse of uterus	9							1	3						4	1						
Normal pelvic organs	25	2	3						10	4	1	1			1	1			2			
Total	159	5	6		2	(1)		4	45	5	2	6	(7)	(3)	27	25			3	(7)	(2)	29

*NOTE: Endometrial polyps and carcinoma are included in parentheses since they represent local conditions and not the character of the endometrium itself.

base and none of the gross anatomic characteristics of a polyp with a pedicle. There is no reason to suppose that all types of endometrial gland hyperplasia are directly or immediately caused by the estrogenic hormone, and there is much to favor an opposite viewpoint.

SUMMARY OF ENDOMETRIAL FINDINGS

The endometrium of the cases of cancer of the cervix, vulva or vagina were available in a few cases only, and that associated with carcinoma of the corpus had been previously reported upon (Taylor). Endometrial specimens were available in 99 of the remaining cases.

Atrophy was the condition present in 75, or approximately three-fourths of the cases. This was the finding in 4 of 13 patients under 50 years, in 45 of 58 patients between 50 and 59, and in 25 of 28 patients after 60.

A nonatrophic endometrium was present 11 times, or in 6 of 13 patients under 50 and in 5 of 58 patients between 50 and 59 years. It was never observed after 60 years of age. This indicates that some years are required in many cases before atrophy recognizable in curetted material develops, or possibly that recrudescences of minor ovarian activity may occur. Its absence after 60 is noteworthy.

An endometrium showing more or less marked signs of a corpus luteum effect was noted twice in women in their fifties, but in both there had been a delayed menopause. In no case was a premenstrual endometrium observed after more than one year of amenorrhea.

Hyperplasia of the endometrium, as the name is now used, is probably still applied to a somewhat heterogeneous group. In this series of cases hyperplasia was noted twice among the 13 endometrial specimens of patients under 50 years of age. These were probably instances of the typical endometrial hyperplasia of the premenopause years and fall in this group of postmenopause cases only because the definition of the menopause was a clinical one. There were 6 patients with hyperplasia in the fifties and 3 in the sixties. Of these, four were associated with a tumor of the granulosa cell group and hence easily explained. Two occurred with pseudomucinous tumors of the ovary, and although manifesting less typical changes than those associated with the granulosa cell tumors, still they were decidedly not atrophic. This hyperplasia is possibly the result of a general hyperemia in the pelvis from the presence of the tumor, possibly the result of substances elaborated by the cysts or by activated ovarian cells in the walls of the cysts. Finally there were three cases of hyperplasia with no demonstrable cause. Certain characteristics of these suggest that they may be of more neoplastic character than the hyperplasia of earlier years, and less immediately dependent upon ovarian stimuli.

In an earlier paper (Taylor) the association of hyperplasia and carcinoma of the endometrium was reported in 15 out of 34 cases of corpus carcinoma in which areas of noncancerous endometrium were available for study. Novak and Yui noted 25 such associations of

hyperplasia and carcinoma in 64 similar cases. It would be hard to imagine any other precursor to cancer of the corpus than some form of glandular hyperplasia.

CONCLUSIONS

Among 406 gynecologic cases admitted to the hospital for vaginal bleeding after the menopause, some type of malignant tumor was present in approximately 63 per cent.

Benign tumors of the uterus and ovary were the lesions chiefly responsible for the symptom in 17 per cent of the cases. Of special interest was the association of hyperplasia of the endometrium with typical cystic pseudomucinous tumors of the ovary in two instances.

Inflammatory lesions, usually in the cervix or vagina, were the apparent cause of bleeding in 11 per cent.

In the remainder, or about 8 per cent, no gross lesion to explain the bleeding was present in the pelvis. Several of this group showed evidence of a late ovarian effect on the endometrium or of an endometrial hyperplasia due to this or other causes. These instances of hyperplastic changes in the postmenopausal endometrium are important as possible precancerous lesions.

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A CHEMICAL TEST FOR PREGNANCY APPLIED TO THE DETERMINATION OF ESTRIN IN THE URINE OF NORMAL AND TOXEMIC PATIENTS IN THE LAST TRIMESTER OF PREGNANCY

II. Application of a Short Chemical Method; and Administration of Theelin* in Late Toxemias of Pregnancy

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In a previous paper[8] we reported results of the chemical determination of estrin in the urine during the last trimester of pregnancy from a series of 60 hospitalized patients. We were able to establish levels of estrin excretion in normal late pregnancy, and to show a definite lowering of these levels in chronic nephritis complicating pregnancy, and in pre-eclampsia.

This study was undertaken to collect more data in this field; to apply a modified chemical procedure[17] for the detection of estrin; and to observe the effects of theelin administration in patients suffering from the late toxemias of pregnancy.‡

METHODS

Toxemic patients admitted to the University Hospital in the last trimester of pregnancy were studied carefully by frequent examinations of urine, blood pressure, eye grounds, blood chemistry, and kidney

*The theelin used in this investigation was provided through the courtesy of Parke, Davis and Co.

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‡The following is the classification of the late toxemias of pregnancy as accepted in our clinic: pre-eclampsia, eclampsia, and chronic nephritis complicating pregnancy.

function. Twenty-four-hour urine specimens were collected and estrin determinations made. A few normal cases (Table I) were included in order to establish normal levels of estrin excretion.

All cases of toxemia were subjected to the routine treatment of the clinic which included absolute bed rest; limitation of fluids to 1,500 c.c. per day (in the presence of edema, and unlimited fluids in its absence); low-protein salt-free diet; magnesium sulphate by mouth; and 50 per cent glucose and 10 per cent magnesium sulphate intravenously, and morphine as required in exacerbations. Other factors in treatment such as the administration of sedatives; induction of labor either medically or by amniotomy; cesarean section; and sterilization, all varied as indicated.

Only a few cases were private, the majority being service admissions from our out-patient department. Nearly all patients were given prenatal care in our clinic where they had been reporting for from two weeks to eight months previous to their admission to the hospital.

No cases of true eclampsia appear in this series, because it was impossible to obtain complete twenty-four-hour urine specimens.

No patient with pre-eclampsia from our own clinic later developed eclampsia.

TABLE I. SIX NORMAL CASES

CASE	AGE	COLOR	PARITY	DURATION OF PREG. WHEN URINE OBT. IN WEEKS	F.N.*	BABY
40	22	W	1-0-0-0†	40	101	F.T.L.*
6	32	B	3-0-0-3	40	96	F.T.L.
1	21	B	2-0-1-2	40	91	F.T.L.
42	20	B	0-0-0-0	38	87	F.T.L.
51	21	W	1-0-0-1	36	75	F.T.L.
46	34	B	10-0-1-11 (twins)	36	73	F.T.L.

*F.N., ferric chloride number; F.T.L., full-term living baby.

†The first figure represents the number of full-term children whether alive or stillborn; the second, the number of prematures; the third, the number of abortions (before the twenty-eighth week); and the fourth shows the number of living children.

PROCEDURE

A modification of the Schmulovitz and Wylie test[9] for the chemical diagnosis of pregnancy by the detection of estrin in the urine was devised by one of us (H. B. W.). A separate publication[17] is planned to describe this test in detail. Briefly, this procedure follows the principles of the original test[9] with a few minor changes, but uses only one-tenth of the twenty-four-hour specimen. A marked reduction in the time required for the laboratory performance of this test, of from twenty-four to thirty hours to four hours, has thereby been achieved.

The essential principle of the chemical test for pregnancy ". . . consists in the extraction of estrin from the urine with ether and its detection by coupling with diazotized paranitroanaline to form a deep-colored azo dye. . . ."[9]

Estrin excretion is expressed in terms of the "ferric chloride number" (F.N. as shown in Tables I to V) which is obtained as follows: ". . . the final colored alcoholic layer containing the estrin extracted from the specimen is filtered into a colorimeter cup and set at 10 mm., and is compared with a standard 33 per cent ferric chloride solution, the reading of which is the 'ferric chloride number.'"[8]

In this short procedure the final reading in millimeters is multiplied by 10 and the factor 9 (the blank error is 1 mm.) is subtracted to give the final "ferric chloride number" (F. N.).

Each specimen in this series was examined by the short method using the same technique throughout.

Estrin determinations were made on the specimens from the cases shown in Table V soon after admission. Similar tests were made on one-tenth of each twenty-four-hour specimen following each of 3 theelin injections (except in Case 58). The patients were carefully observed clinically to note any unfavorable reactions or any improvement in their condition which might have been attributed to theelin administration.

Goldberger[5] has defined free and combined "estrins" according to Marrian's concept. Free "estrins" are those that can be extracted with ether from the untreated urine, and combined "estrins" are extractable with ether only after hydrolysis of the urine by acidification and boiling. Since all specimens were hydrolyzed our estimations are based on the total estrin output in twenty-four hours.[17]

DISCUSSION

In Tables I to III the data are arranged under the following headings: case number, age, color, parity of the patient, duration of pregnancy in weeks at the time when the twenty-four-hour specimen was obtained for analysis, "ferric chloride number" (F.N.), and the outcome of the pregnancy (F.T.L., full-term living baby; F.T.D., full-term baby who was stillborn, or born alive but did not survive the neonatal period; L, premature baby who survived the neonatal period; and D, premature baby who was stillborn, or born alive but did not survive the neonatal period).

Table IV is a summary of Tables I to III, and includes a comparison of the data of the present series of cases with those of the first series.[8]

Table V gives a summary of the data of the cases in which theelin was administered.

TABLE II. TWENTY-SIX CASES OF CHRONIC NEPHRITIS COMPLICATING PREGNANCY

CASE	AGE	COLOR	PARITY	DURATION OF PREG. WHEN URINE OBT. IN WEEKS	F.N.	BABY
31	35	W	3-0-0-3	40	63	F.T.L.
5	32	W	5-0-1-5	37	61	F.T.L.
24	36	B	2-1-0-1	30	61	F.T.L.
37	28	W	3-0-0-3	40	61	F.T.L.
53	28	B	4-4-0-4	40	61	F.T.L.
21	28	W	5-2-1-5	40	58	F.T.L.
57	31	B	4-0-2-4	38	57	F.T.L.
38	28	W	4-0-0-3	40	56	F.T.L.
22	19	B	1-0-0-1	39	55	F.T.L.
45	32	B	3-1-1-3	36	53	F.T.L.
56	30	B	2-0-1-2	38	53	F.T.L.
60	23	W	0-0-0-0	35	52	F.T.L.
3	24	B	0-2-0-0	28	51	32D*
15	19	B	0-0-0-0	34	51	34D
48	38	B	7-0-2-5	32	51	32L†
58	24	W	0-0-0-0	34	50	34L
54	28	B	2-0-0-2	38	49	F.T.L.
9	25	B	5-0-0-5	41	39	F.T.L.
16	19	B	1-1-0-2	38	40	F.T.L.
50	27	W	3-1-0-3	38	33	F.T.L.
17	24	B	0-0-0-0	40	32	F.T.L.
8	26	B	1-0-0-1	40	31	F.T.L.
18	14	B	0-0-0-0	38	31	F.T.L.
13	16	B	0-0-0-0	36	28.5	F.T.L.
7	20	W	0-0-0-0	24	23	F.T.L.
19	21	W	0-0-0-0	30	23	30L

*Weeks, dead. †Weeks, living.

Normal Cases.—The six cases shown in Table I were all normal in that they showed no clinical evidences of toxemias of pregnancy. They were admitted to the hospital near term, not in labor, for the following reasons:

Contracted pelvis	3 cases
Previous dystocia	2 cases
Recent operation for rectal stricture	1 case

One patient was a primigravida; 2 were white and 4 were colored.

The average duration of pregnancy at the time the twenty-four-hour specimens were obtained was 38.33 weeks, while the average "ferric chloride number" (F.N.) was 87.16, the highest being 101 and the lowest 73. From Table IV we see that the average "ferric chloride numbers" in the normal group in the first series[8] and in the present series are very close, and, that in the present series the range of the "ferric chloride number" is more restricted than in the former series, but the average is higher.

TABLE III. TWENTY-SIX CASES OF PRE-ECLAMPSIA

CASE	AGE	COLOR	PARITY	DURATION OF PREG. WHEN URINE OBT. IN WEEKS	F.N.	BABY
28	23	W	0-0-0-0	32	70	F.T.L.
33	17	B	0-0-0-0	38	56	F.T.L.
29	18	B	0-0-0-0	36	55	F.T.L.
11	16	B	0-0-0-0	37	51	F.T.L.
27	24	W	0-0-0-0	39	46	F.T.L.
30	32	B	1-0-0-1	38	43	F.T.L.
35	24	W	0-0-0-0	40	42	F.T.L.
49	21	B	0-0-1-0	40	42	F.T.L.
32	25	W	0-0-0-0	37	41	F.T.L.
39	25	W	0-0-0-0	38	41	F.T.L.
41	18	W	0-0-0-0	38	40	F.T.L.
43	20	W	0-0-0-0	39	40	F.T.L.
44	16	B	0-0-0-0	36	40	F.T.L.
55	18	W	0-0-0-0	34	40	38L
52	18	B	0-0-0-0	35	37	F.T.L.
59	21	W	0-0-0-0	39	37	F.T.L.
2	16	B	0-0-0-0	35	36	F.T.L.
12	18	W	0-0-0-0	40	36	F.T.L.
36	21	W	0-0-0-0	38	36	F.T.L.
47	15	B	0-0-0-0	28	36	F.T.L.
14	22	W	0-0-0-0	40	33	F.T.L.
4	15	B	0-0-0-0	34	31	F.T.L.
20	30	B	0-0-0-0	36	30	F.T.L.
34	38	W	0-0-0-0	40	30	F.T.L.
26	18	B	0-0-0-0	40	30	F.T.D.
25	31	W	0-0-0-0	38	22	F.T.L.

TABLE IV. SUMMARY OF TABLES I TO III. COMPARISON OF RESULTS WITH LONG AND SHORT METHOD

		AVERAGE F.N.	F.N. RANGE	TOTAL NO. OF CASES	AVERAGE DURATION OF PREGNANCY, WEEKS
Normal	A*	83.30	152.00-56.60	21	36.00
	B	87.16	101.00-73.00	6	38.33
Chronic nephritis	A	51.67	64.00-40.00	19	37.10
complicating preg.	B	47.05	63.00-23.00	26	36.30
Pre-eclampsia	A	36.87	45.00-28.50	20	38.10
	B	40.03	70.00-22.00	26	37.11

*A, Series originally reported.[8] B, Present series.

Cases 51 and 46 (Table I) had been diagnosed as having chronic nephritis complicating pregnancy in their previous pregnancies, but in each case the pregnancy reported here showed no toxic signs or symptoms. It may be significant that these two cases gave the lowest "ferric chloride numbers," which may have indicated some residual pathology from the toxemia in the previous pregnancy even though the present pregnancy was clinically normal.

All patients in the normal series were delivered of full-term living children who survived the neonatal period.

Chronic Nephritis Complicating Pregnancy.—The 26 cases of chronic nephritis complicating pregnancy shown in Table II were characterized by: albuminuria, nitrogen retention and elevation of blood pressure at least one month before delivery which persisted at levels above normal after delivery. Many showed edema and pathologic eye grounds. One patient (Case 56, Table II) died at home about one month after discharge from the hospital of generalized carcinomatosis which had developed from malignant breast tumor. (This patient and Case 34 [Table III] who also died, represent an uncorrected maternal mortality of 3.4 per cent for the entire series of 58 cases.) All these patients were admitted to the hospital because of toxemia. Eight were primigravidas. There is a definite increase in the number of primigravidas in this series of cases of chronic nephritis complicating pregnancy as compared to our previous series[8] in which there was only one primigravida in 19 cases. Patients in this series had toxic symptoms and findings to a varying degree for from six weeks to six months prior to delivery. Ten patients were white and 16 were colored.

The average duration of pregnancy when the twenty-four-hour urine specimens were obtained was 36.3 weeks, while the average "ferric chloride number" (F.N.) was 47.05, the highest, 63.0, and the lowest, 23.0 (Table IV). Thus there was a wider range of F.N. and a lower average in this series than in the first (see Table IV).

In the present series there were 21 full-term living children, 32- and 34-week stillbirths, and 30-, 32-, and 34-week living babies who survived the neonatal period.

No attempt was made to subdivide these patients into those who had suffered from chronic nephritis prior to the first pregnancy or those developing chronic nephritis during the course of subsequent repeated pregnancies, nor to differentiate between the types of chronic nephritis.

Definite lowering of estrin excretion in chronic nephritis complicating pregnancy in the previous series[8] has been confirmed in the present series as shown in Table IV.

There is, however, no overlapping of the F.N. of this group with the F.N. of the normal group as was observed in the first series. Thus the normal cases are more sharply defined from the two toxemic groups. On the other hand, there is considerable overlapping of the F.N. of the nephritic group with that of the series of cases of pre-eclampsia.

Pre-eclampsia.—Table III represents a series of 26 cases of pre-eclampsia characterized by: sudden elevation of blood pressure, sudden appearance of albumin in urine previously normal, increased uric acid retention, and by the sudden onset of subjective symptoms in late pregnancy varying from edema of the feet and ankles to edema of the face and hands, abnormal weight gain, nausea and vomiting, headache, precordial pain, and visual disturbances. These patients were admitted to the hospital because of toxemia. Only 2 of these patients were multigravidas. Fourteen patients were white, 12 were colored. The average duration of pregnancy when the twenty-four-hour urine specimens were obtained was 37.11 weeks; while the average "ferric chloride number" (F.N.) was 40.03, the highest, 70.00, and the lowest, 22.00 (Table IV).

In this series there was one full-term baby who did not survive the neonatal period, and one 38-week living baby who was discharged in good condition. The remainder of these pregnancies terminated in the births of full-term living infants, all of whom survived the neonatal period.

One patient in this series (Case 34, Table III) was an unregistered case who was admitted because of fulminating pre-eclampsia. Elective laparotrachelotomy was performed and the patient died four days later of peritonitis due to infection by hemolytic streptococci.

Two other patients in this series (Cases 26 and 55, Table III) with fulminating pre-eclampsia were delivered by elective laparotrachelotomy with good results.

Case 28 (Table III) was a primigravida admitted at the thirty-second week of her pregnancy because of a mild pre-eclampsia. The "ferric chloride number" (F.N.) was 70 at that time. On routine treatment the patient improved and was discharged. At term the patient was readmitted in active labor and gave no evidence of toxic manifestations throughout her stay in the hospital. This case is mentioned to show a mild pre-eclamptic with a "ferric chloride number" (F.N.) above the range for the remainder of the group (Table III).

We again found a definitely lowered level of estrin excretion in pre-eclampsia (Table IV). The difference between the average "ferric chloride number" (F.N.) in this group and that of the first series[8] is not great, and there is little difference between the estrin excretion in this group of pre-eclamptic patients and the group of patients suffering from chronic nephritis complicating pregnancy (see Table IV). Therefore, using the short method, we were not able to differentiate the two groups of cases as sharply as was possible in the original study. The "ferric chloride number" range for the two groups of cases of toxemia is practically the same, while the normal group stands alone with the exception of Case 28 (Table III).

We do not claim at present, however, that it is possible with our methods to correlate the estrin excretion with the severity and type of toxemia, although it may be fair to state that it seems possible to differentiate normal pregnancy from the two pathologic groups under discussion.

Theelin Administration.—Before administering theelin to any of our patients, a very careful search of the literature was made to determine the safety of this procedure. Mazer[6] and his co-workers, after injecting estrogenic substance in divided doses, concluded that it produced no significant changes in blood pressure, basal metabolism, body weight, blood count, and blood chemistry. Witherspoon,[16] and Robinson[7] and his colleagues found that the administration of estrin near term might or might not induce premature labor, but that it was not a reliable means of induction.

Zieman[18] warns against side reactions as urticaria, generalized dermatitis, and anaphylactic shock following intragluteal injections of theelin in oil (1 c.c. containing 1000 international units). No reactions were observed in our cases.

Geschickter, Lewis, and Hartman[4] found a depressing effect of estrin on the basal metabolic rate by administering the "estrin hormones" to patients with hyperthyroidism.

After an extensive search of the literature, Dodds[2] failed to find any incontrovertible evidence that estrogenic substances are carcinogenic. Discussing the relationship between estrogenic and carcinogenic substances, Frank[3] states that as yet no convincing contraindications to the clinical employment of estrogenic substances have been discovered.

Steinkamm and Giesen[15] observed that as yet it had not been proved that estrogenic substance reduces blood pressure. Their studies were made on nonpregnant women.

It has been suggested by Smith and Smith,[12] and Smith and Kennard[11] that the excessive amounts of prolan in the blood and urine of toxemic women have their origin in the placenta. Smith and Smith[12] further suggest that the continued overproduction of prolan by the placenta is a possible causal factor in the etiology of the toxemias of late pregnancy. These same authors[13, 14] have called attention to the mutually antagonistic action of prolan and estrin and suggest estrin as an experimental therapeutic measure in these toxemias.[14] At the onset of our second series of observations it was our purpose to test this action of theelin in a few cases (see Table V). Regardless of the origin of excess prolan in the late toxemias, it seemed logical to us to administer theelin in such cases, not as replacement therapy for the lowered estrin level, but to inhibit the action of excess prolan.

TABLE V. SUMMARY OF CASES IN WHICH THEELIN WAS ADMINISTERED

CASE	AGE	COLOR	PARITY	DIAGNOSIS	INTERVAL BET. LAST DOSE THEELIN AND ONSET OF LABOR	HOURS LENGTH LABOR	BABY	APPARENT EFFECT OF THEELIN ON TOXEMIA	F.N.*	THEELIN INT. U.
36	21	W	0-0-0-0	Pre-ecl.	32.50 hr.	7	F.T.L.	None	36	30,000
41	18	W	0-0-0-0	Pre-ecl.	10 days	8.5	F.T.L.	None	40	30,000
43	20	W	0-0-0-0	Pre-ecl.	31.00 hr.	15	F.T.L.	None	40	30,000
44	16	B	0-0-0-0	Pre-ecl.	24 days	14.5	F.T.L.	None	40	30,000
50	27	W	3-1-0-3	Neph.	10 days	5	F.T.L.	None	33	30,000
51	21	W	1-0-0-1	Norm.	24 days	8	F.T.L.	None	75	30,000
52	18	B	0-0-0-0	Pre-ecl.	31 days	12	F.T.L.	None	37	30,000
58	24	W	0-0-0-0	Neph.	3.00 hr.	11	34L	None	50	10,000
59	21	W	0-0-0-0	Pre-ecl.	15.50 hr.	6.75	F.T.L.	None	37	30,000
60	23	W	0-0-0-0	Neph.	30 days	4	F.T.L.	None	52	30,000

*Previous to theelin administration.

The immediate problem in the treatment of these cases was to determine what product to use and in what dosage it should be administered. Our studies were made on the output of total estrin in twenty-four hours. It was arbitrarily decided to administer a preparation of so-called "free estrins"[5] in an oil solution to permit of gradual absorption. Urinary excretion of estrogenic substance at term in normal pregnancy has been determined by various investigators at about 6,000 rat units in twenty-four hours. Since our series of toxemic patients in the last trimester of pregnancy excreted approximately only one-half the normal amount (Table IV) it was decided to administer 3,000 rat units of estrogenic substance per day for three successive days. Larger doses were decided against to avoid the possibility of exaggerating existing symptoms, because the tolerance of these patients to this substance was unknown. Shute,[10] in treating cases of late toxemia with estrin, observed a picture strongly suggestive of abruptio placentae in one of his patients following estrin administration. He therefore suggests that during pregnancy estrin should be used quite cautiously and in small dosage. Shute administered massive doses of estrogenic substances.

Theelin was used in this investigation (1 c.c. ampoule containing 10,000 international units which is approximately 3,000 Doisy rat units).

The cases chosen for hormone therapy (Table V) were not especially selected from among the others. One normal case was included for comparison (Case 51, Table V).

Nine of the 10 ward cases shown in Table V were given 10,000 international units of theelin intramuscularly on 3 successive days (30,000 international units in all), while the patient in Case 58 received only one injection of 10,000 international units since labor began three hours later. All patients given theelin were kept on the routine treatment except that oral administration of magnesium sulphate was discontinued in order that accurate twenty-four-hour urine specimens could be collected.

The injections were given intragluteally followed by several minutes of gentle massage. None of the patients complained of pain or discomfort other than that caused by the entrance of the needle or by the pressure of the injection, both of which were momentary. No side reactions were observed. The patients were given to understand that these injections were a part of the routine treatment.

The cases were carefully observed for blood pressure changes at least every four hours (except the patient in Case 51 who was normal), and by frequent eye

ground, blood chemistry, kidney function, and urine examinations. The general condition and the progress were also carefully noted.

Eight of these patients were white while 2 were colored. Eight were primigravidas. Six were pre-eclamptic, 3 were noted as having chronic nephritis complicating pregnancy, and 1 was normal.

The latent period between the last injection of theelin and the onset of labor varied from three hours (Case 58, Table V only 1 injection given) to thirty-one days. Only 4 of these patients went into labor before ten days following the last injection, and in these the hormone possibly may have had some part in the induction. In 2 cases (Cases 50 and 51) it was necessary to induce labor by amniotomy.

The longest labor in the series was fifteen hours, the shortest, four hours, while the average was 9.17 hours. From our data it is impossible to state definitely whether or not the theelin influenced the length of labor, but it is interesting to note the short average duration of labor, even in this small series, especially since 8 of the 10 patients were primigravidas.

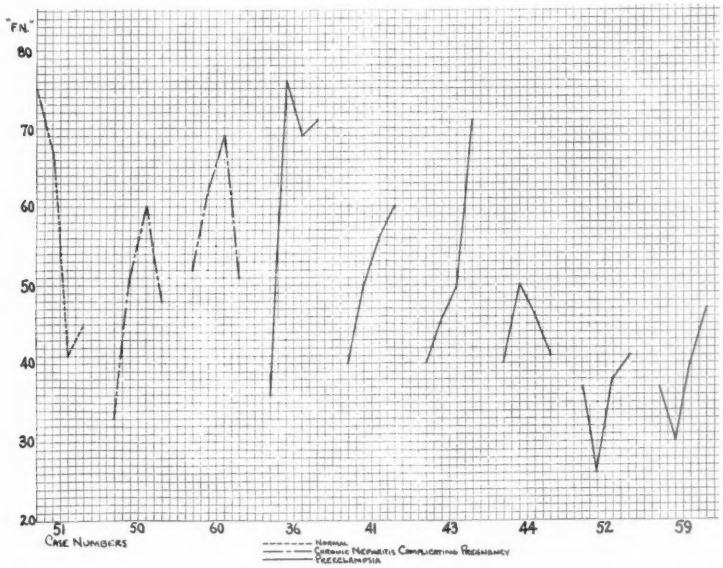

Chart 1.—Estrin excretion.

All but one of the patients in this series were delivered of full-term living children who survived the neonatal period. The patient in Case 58 was delivered of a thirty-four-week premature baby who survived the neonatal period. No untoward effects of the theelin upon any of these babies were noted.

There was no delay in uterine involution in any of these patients, nor was there any acceleration in this process.

After reviewing these cases critically we cannot say that there was any improvement in any of the 10 patients which could be ascribed directly to the hormone therapy. It is possible that the short average duration of labor may have been the result of this therapy. Failure to observe clinical improvement may have been due to inadequate dosage or to too late administration. The possible advantages of administering theelin to patients with decreasing estrin excretion before clinical manifestations of toxemia appear should certainly be kept in mind.

Chart 1 shows individual curves representing the estrin excretion of the 9 patients each of whom received 3 theelin injections. The first reading in each curve is the "ferric chloride number" (F.N.) obtained from examination of a twenty-four-hour specimen before hormone therapy was instituted, while the other three points in each curve represent the "ferric chloride numbers" (F.N.) of twenty-four-hour speci-

mens obtained during the twenty-four-hour period immediately following each injection. Cases 50 and 60 represent patients with chronic nephritis complicating pregnancy and their curves are roughly similar. Case 51 is a normal patient and is interesting in that the estrin excretion was apparently markedly decreased even though theelin was being administered. Four of the 6 curves of pre-eclamptic patients show an initial rise (Cases 36, 41, 43, 44), while 2 (Cases 52, 59) show an initial fall in estrin excretion, with a secondary rise. Due to lack of uniformity in these results it is impossible to draw any accurate conclusions. Variations such as these might be at least partially explained on the cyclic excretion of estrin throughout pregnancy as reported by Browne and Venning.[1] There was no correlation possible between estrin excretion and clinical findings (Tables I to III and Chart 1).

SUMMARY

1. Further data are presented showing a definitely lowered level of estrin excretion in the urine in a series of cases of the late toxemias of pregnancy.

2. A short chemical procedure for detecting estrin in urine has been developed and was applied to the analysis of all specimens in this series. A test by this method may be completed in four hours.

3. Pre-eclampsia, eclampsia, and chronic nephritis complicating pregnancy are considered the late toxemias of pregnancy.

4. Fifty-eight patients in the last trimester of their pregnancies were carefully studied clinically and complete twenty-four-hour urine specimens were examined for estrin. Estrin excretion expressed as "ferric chloride numbers" (F. N.) gave averages: for 6 normal cases, 87.16, for 26 patients with chronic nephritis complicating pregnancy, 47.05; and for 26 cases of pre-eclampsia, 40.03.

5. In this series normal cases have been sharply delimited from the toxemic groups on the basis of estrin excretion. No cases of true eclampsia appear in this series.

6. As concerns estrin excretion the line of demarcation between chronic nephritis complicating pregnancy and pre-eclampsia is not as sharp as in our former series in which the original procedure was used.

7. Nine patients received 10,000 international units of theelin intramuscularly on each of 3 successive days, and complete twenty-four-hour urine specimens on each of these days from each patient were examined for estrin (Chart 1).

8. No accurate conclusions may be drawn from this series concerning estrin excretion in the late toxemias of pregnancy following the intramuscular administration of theelin.

9. It is possible that the short average duration of labor in the 9 patients treated with theelin may have been the result of this therapy.

10. In the cases of late toxemias of pregnancy in this series to whom theelin was administered, in the dosage and in the manner herein described, no improvement was found which could be directly ascribed to the hormone therapy.

The authors wish to express their sincere appreciation to the resident and nursing staffs of the Obstetrical Service of the University Hospital for their indispensable aid in obtaining the necessary specimens.

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Lombard and Greene Streets

STUDIES ON THE CIRCULATION IN PREGNANCY

III. Blood Volume Changes in Normal Pregnant Women

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IN ANY consideration of the altered physiology of the circulation during normal pregnancy, notably the low level of the solid constituents of the blood, the diminished viscosity of the blood, the changes in cardiac output and velocity of blood flow, and the frequent occurrence of edema, it is important to know what variations, if any, occur in the plasma and blood volume. Such information is likewise useful in evaluating certain pathologic conditions frequently associated with pregnancy; particularly cardiac disease and the "toxemias" of pregnancy.

Dieckman and Wegner, who contributed a valuable blood volume study in 1934,[1] pointed out in their review of the literature the conflicting findings of previous investigators in this field. They cited important criticisms: First, none of the earlier studies included an adequate number of determinations on the same individuals during the ante- and post-partum periods, conclusions having been drawn from the analysis of disparate groups; and second, the methods used were various and of doubtful accuracy, in some instances in technique, elsewhere in calculations based on the patients' weights without due regard to the undeterminable quantity of the uterus and its contents and to maternal edema. It should be emphasized, in addition, that it is unlikely that a reliable estimate of the blood volume changes occurring in pregnancy can be obtained by the comparison of single

observations on many individuals in the several periods of gestation with the average normal nonpregnant volume whether absolute or in terms of body weight, since the range of volume in normal persons is great.

Dieckman and Wegner[1] found an increase in the plasma and total blood volumes in the second trimester of pregnancy and at term, as compared to the first trimester which amounted to a maximum of 25 per cent for plasma and 20 per cent for total blood volume. They also reported a post-partum decrease, not always manifest early in the puerperium, as compared to the last ante-partum determination (actually, however, in their Group A patients, followed throughout pregnancy and the puerperium, 6 of the 13 showed a higher post-partum total blood volume than at the last ante-partum observation!). The plasma volume increase was relatively greater than that of the red cell volume. These authors, while they were of the opinion that repeated determinations on the same individual checked closely and were significant, conceded that the Keith-Rowntree method,[2] which they used, was liable to distinct errors.

The use of the original Keith-Rowntree method in this clinic produced such variable results that no definite conclusions could be drawn as to the behavior of the blood volume in pregnant women.*

When, therefore, a new method which satisfactorily avoids the pitfalls of the earlier dye methods became available by the work of Gregersen, Gibson, and Stead,[3] another study of the blood volume in pregnancy seemed indicated.

PROCEDURE

The subjects for this study were obtained from the prenatal clinic of the Boston Lying-in Hospital, and were chosen at random, the only basis of selection being the duration of pregnancy and freedom from medical or obstetric complications. Observations were made at frequent intervals throughout pregnancy, usually about six weeks apart, and at least once post partum, usually at two weeks. The observations on individual patients varied between two and six, with an average of four.

The data usually taken at each visit were: weight, arterial blood pressure, pulse and respiratory rates, venous pressure, circulation time, subcostal angle, hemoglobin, red blood cell count, hematocrit, vital capacity, blood volume, and occasionally, basal metabolic rate. Every patient at each visit received a careful physical examination of the heart, lungs, abdomen, and extremities.

All patients were studied under basal conditions of fasting and resting. Blood volume and venous pressure observations were preceded by at least thirty minutes' bed rest, and circulation time measurements by at least sixty minutes' bed rest. Vital capacities were determined according to the routine described fully in a separate paper.[4]

In presenting our data, the duration of gestation has been calculated back from the actual day of delivery, the duration of a full-term pregnancy being taken as 280 days, or ten lunar months.

METHODS

With the exception of the blood volume method which is described below, the other determinations were carried out exactly as described in a previous report.[5]

Blood volumes were determined by the method developed by Gregersen, Gibson, and Stead,[3] as adapted to clinical use by Gibson and Evans,[6] in which the plasma

*In approximately 100 attempts, 75 "satisfactory" observations on the blood volume were made on normal pregnant women at the Boston Lying-in Hospital by Dr. Mandel E. Cohen. The results from this study tended to show that the total blood volume increased during pregnancy and diminished after delivery. It was felt by him, however, since checks on the same sample were so difficult to obtain and since the percentage error in the method was so great, that the results of the study were unreliable.

volume is actually determined and the total blood and red cell volumes calculated from the plasma volume and the hematocrit value. This method employs a blue azo dye, Evans Blue (T-1824),[7] and is a modification of the Keith-Rowntree method.[2]

It minimizes errors inherent in earlier techniques, resulting from variations in the time required for complete mixing of the dye in the blood stream, where volume calculation is based on the dye concentration of a single sample taken three to six minutes after dye injection. Furthermore, incalculable errors arising from variations in the rate of disappearance of dye from the blood stream are eliminated. Colorimetric estimations of the dye concentration of serum samples are made with the spectrophotometer, thus eliminating errors arising from inequality in dye concentration between standard and samples.[8] The use of a blue dye minimizes errors due to hemolysis of samples and affords an accurate spectrophotometric method of correcting for such occasional hemolysis as may occur.

Minor modifications of the method as described by Gibson and Evans[6] were employed; the infiltration of skin at the site of venipuncture with procaine without adrenalin (gratefully acknowledged by the patients) and, occasionally, the use of 0.5 per cent sodium citrate in normal saline solution to inhibit clotting in the needle between sampling.

No systemic reactions to the dye, nor evidences of vein damage by it were encountered. Accidental injection of the dye extravenously produced local discoloration, but little or no discomfort and no tissue reaction or necrosis. None of the patients showed sufficient generalized coloration of the skin and subcutaneous tissues from the dye (average dose 10 mg.) to be apparent to the casual observer.

Relatively large doses of dye (30 mg.) were given to 6 patients in labor. Spectrophotometric examination of the amniotic fluid and cord serum of 3 showed no dye. In none could dye be detected in microscopic examination of the membranes and placentas prepared by special technique to show the presence of this dye histologically.* It was therefore assumed that the disappearance of the dye from the blood stream is not influenced by passage to the ovum. Evans and Gibson[9] have showed that any influence of occult edema on the accuracy of the blood volume determinations may be disregarded.

Duplicate red blood cell counts and hemoglobin determinations were made from oxalated venous blood (no stasis) obtained at the first venipuncture, using certified pipettes and counting chambers and a Sahli hemoglobinometer calibrated by the oxygen capacity method, so that 100 per cent represents 15.6 gm. of hemoglobin per 100 c.c. whole blood.

RESULTS

The data here presented (Table I) were derived from 56 observations (40 ante and 16 post partum) on 14 patients whose pregnancies were entirely normal. In this group there were 9 primiparas and 5 multiparas, varying in age from 20 to 34 years, with an average age of 25.1 years. One patient in the series who delivered twins, although included in Table I, is not considered in the general analysis.

The plasma volume was actually determined in this study. From it, by means of the hematocrit value, the total blood and cell volumes were calculated. Although for general physiologic purposes the chief concern is the state of the total blood volume, there is special interest in the plasma volume in pregnancy, since there is a reported disproportionate increase between it and the cell volume resulting in the "hydration" phenomenon.

*Sections of the placenta and membranes were prepared according to the method of Dr. Harold L. Weatherford, Dept. of Anatomy, Harvard Medical School, in which tissues were fixed in fluid composed of acetic acid 4.0 c.c., trichloracetic acid 2.0 gm., sodium chloride 0.5 gm., corrosive sublimate 5.0 gm., 37 per cent formalin 20.0 c.c., water 80.0 c.c.; run through paraffin and stained with Mayer's paracarmine in 70 per cent alcohol. The authors are indebted to Dr. Hugh H. Nuckols, resident pathologist, Boston Lying-in Hospital, for these histologic preparations and examinations.

PLASMA VOLUME

There is a progressive increase in plasma volume from early pregnancy through the ninth lunar month, when the maximum is reached. This amounts to an increase of 65 per cent above the average normal nonpregnant value (Chart 1). During the tenth month there is a definite decrease to 50 per cent above the normal nonpregnant level. Post partum this decrease continues so that by the end of the second

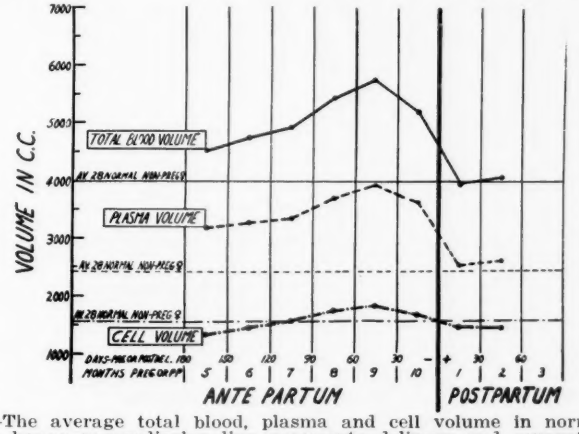

Chart 1.—The average total blood, plasma and cell volume in normal pregnant women. The heavy perpendicular line represents delivery and separates the ante- and post-partum periods. Note that the maximum increase occurs in the ninth lunar month, with a definite diminution before delivery.

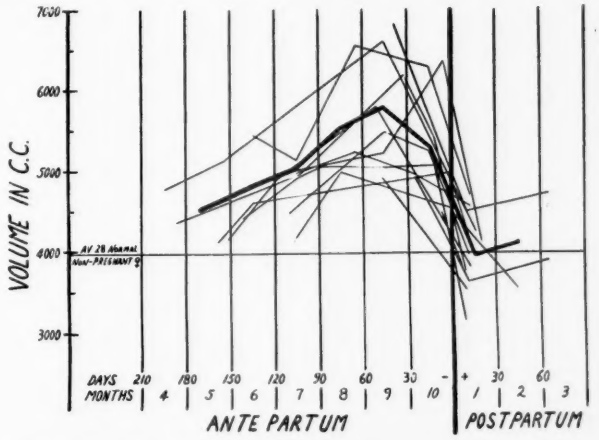

Chart 2.—The total blood volume in normal pregnant women. The fine connected lines represent curves of individual patients; the heavy line represents the curve of average values. The heavy perpendicular line represents delivery and separates the ante- and post-partum periods. Note that all of the ante-partum values are above the average normal nonpregnant value, whereas post partum they group closely about it.

post-partum week the normal nonpregnant level is reached. The plasma volume varied between 2,620 and 4,470 c.c., an average of 3,710 c.c. ante partum and between 2,010 and 3,050 c.c., an average of 2,106 c.c. post partum. The range of plasma volume determined by the same method in a group of 28 normal nonpregnant women of the same age group is from 1,880 to 2,860 c.c., an average of 2,370 c.c.

TABLE I.—THE TOTAL BLOOD, PLASMA AND CELL VOLUMES AND OTHER

CASE	AGE	PARITY	HEIGHT	WEIGHT	"NORMAL" SURFACE AREA	DATE OBSERVED	ANTE PARTUM	POST PARTUM	TOTAL BLOOD VOLUME		PLASMA VOLUME		CELL VOLUME	HEMATOCRIT	HEMO
									OBSERVED	PER KG.	OBSERVED	PER KG.			PER CENT
	YR.		INCHES	KG.	SQ. METERS		DAYS	DAYS	C.C.	C.C.	C.C.	C.C.	C.C.	PER CENT	
1	34	4	63½	82.1	1.77	Oct. 23, 1935	40		6830	83.5	4470	54.7	2360	34.45	
				69.4		Dec. 12, 1935		11	4540	65.4	2920	42.0	1620	35.80	79
				72.2		Feb. 7, 1936		68	4720	65.3	3050	42.2	1670	35.28	63
2	22	1	60½	45.9	1.35	Oct. 29, 1935	161		4090	88.2	2790	60.0	1300	31.82	65
				47.9		Nov. 26, 1935	133		4570	95.7	3200	67.1	1370	29.90	67
				56.4		Apr. 7, 1936	0	0	4970	87.9	3520	62.3	1450	29.08	52
				43.9		Apr. 20, 1936		13	4000	91.0	2590	58.9	1410	35.28	68
3	26	2	64¼	61.0	1.66	Oct. 31, 1935	193		4780	78.5	3600	58.0	1180	30.87	64
				63.4		Dec. 10, 1935	153		5160	81.4	3650	57.7	1510	29.20	60
				68.2		Feb. 12, 1936	90		5960	87.2	4080	59.7	1880	31.50	60
				70.0		Mar. 25, 1936	47		6560	93.7	4550	65.0	2010	30.55	65
				61.1		May 28, 1936		14	4230	69.2	2590	42.4	1640	38.75	76
6	30	1	65	55.3	1.56	Nov. 25, 1935	102		4920	88.6	3360	60.6	1560	31.75	68
				57.5		Jan. 10, 1936	62		5200	90.2	3690	64.0	1510	27.90	52
				58.0		Feb. 8, 1936	26		4970	85.3	3260	56.0	1710	34.43	70
				54.8		Mar. 19, 1936		14	4520	82.6	2680	49.1	1840	40.61	78
				51.0		May 16, 1936		72	----	---	----	---	----	36.00	70
7	24	1	66	53.2	1.58	Dec. 14, 1935	185		4360	82.0	2960	55.7	1400	32.15	62
				60.9		Mar. 5, 1936	104		4900	80.5	3400	55.8	1500	30.60	60
				69.6		May 6, 1936	32		6150	88.3	3720	53.3	2430	31.52	63
				71.7		June 10, 1936	7		5330	74.3	3600	50.2	1730	32.48	65
				64.6		June 29, 1936		12	3770	58.3	2505	38.9	1265	33.48	65
9	23	1	62	48.6	1.42	Jan. 17, 1936	144		4390	90.3	3090	63.4	1300	29.60	58
				51.1		Feb. 14, 1936	106		4870	95.5	3470	68.0	1400	28.75	58
				51.8		Mar. 3, 1936	89		4945	95.5	3500	67.5	1445	29.34	60
				55.0		Apr. 24, 1936	47		4920	89.8	3510	64.0	1410	28.64	55
				58.2		May 28, 1936	13		4970	85.3	3570	61.3	1400	28.20	50
				47.5		June 19, 1936		9	3140	66.3	2110	44.3	1030	32.70	62
10	22	1	65¾	79.3	1.74	Jan. 22, 1936	135		5370	67.7	3570	45.2	1800	33.40	61
				81.5		Feb. 19, 1936	107		5120	62.8	3440	42.3	1680	32.70	66
				84.6		Apr. 1, 1936	65		6525	77.2	4350	51.5	2175	33.20	67
				89.6		May 21, 1936	15		6350	70.9	4350	48.6	2000	31.45	67
				77.3		June 17, 1936		12	4590	59.4	3010	38.9	1580	34.45	66
12	29	2	63¾	47.9	1.45	Jan. 23, 1936	151		4110	85.9	2930	61.3	1180	28.60	56
				50.9		Feb. 24, 1936	119		4840	95.3	3330	65.7	1510	31.19	66
				54.3		May 11, 1936	43		5770	106.3	4020	74.2	1750	30.28	68
				48.5		July 7, 1936		14	3870	79.7	2370	49.0	1500	38.47	77
13	28	1	61½	53.7	1.46	Jan. 27, 1936	109		4070	75.8	2620	48.8	1450	35.59	67
				58.0		Mar. 2, 1936	74		4950	85.6	3120	53.9	1830	37.00	71
				67.0		May 14, 1936	0	0	4530	67.7	2755	41.2	1775	39.13	77
				54.1		June 26, 1936		43	3520	65.0	2290	42.2	1230	35.04	70
14	24	2	63½	65.9	1.50	Feb. 3, 1936	7		4480	68.1	2800	42.6	1680	37.40	76
				58.2		Feb. 21, 1936		11	3860	66.3	2580	44.3	1280	33.13	66
15	20	1	63	57.5	1.50	Feb. 3, 1936	141		4530	78.8	3120	54.3	1410	31.20	65
				60.4		Mar. 14, 1936	112		4430	73.7	3040	50.4	1390	31.31	68
				61.2		May 9, 1936	46		5470	89.5	3900	62.7	1570	30.00	66
				63.0		June 6, 1936	18		5280	83.8	3660	58.4	1520	30.50	65
				53.3		July 7, 1936		13	3950	74.1	2400	45.1	1550	39.03	78
16	24	3	61½	54.8	1.43	Feb. 5, 1936	47		4920	90.0	3340	61.1	1580	32.10	61
				49.5		Apr. 3, 1936		11	3530	71.2	2010	40.6	1520	43.00	77
17	25	1	62½	72.3	1.59	Feb. 6, 1936	20		4910	68.1	3440	47.7	1470	30.00	62
				60.5		Mar. 9, 1936		12	3580	59.1	2315	38.2	1265	35.30	66
				59.6		Apr. 30, 1936		64	3880	65.2	2540	42.7	1340	34.51	66
18	22	1	65	58.2	1.61	Feb. 13, 1936	105		4980	85.6	3250	55.8	1730	34.80	73
				65.0		Apr. 9, 1936	49		5120	78.8	3790	58.3	1330	33.62	62
				71.2		May 22, 1936	6		6310	88.6	4240	59.6	2070	32.67	65
				59.1		June 17, 1936		20	4090	69.2	2520	42.7	1570	38.40	69
19	24	3	66½	74.5	1.75	Feb. 27, 1936	5		7470	100.5	5050	67.8	2420	32.40	64
				59.6		Mar. 16, 1936		13	4220	70.7	2370	39.7	1850	43.90	78

ASPECTS OF THE BLOOD AND CIRCULATION IN NORMAL PREGNANT WOMEN

GLOBIN	RED BLOOD COUNT	ARTERIAL PRESSURE		VENOUS PRESSURE (ARM)	CIRCULATION TIME			SUBCOSTAL ANGLE	VITAL CAPACITY OBSERVED	EDEMA	DYSPNEA	
GRAMS	MILLIONS PER C. MM.	SYSTOLIC MM. HG.	DIASTOLIC MM. HG.	CM. H_2O	ARM TO CAROTID SEC.	PULMONARY SEC.	VENOUS SEC.	DEGREES	C.C.			REMARKS
----	----	130	82	10.0	--	--	--	110	3120	+	+	Delivered Dec. 1, 1935
12.30	4.70	138	88	---	--	--	--	90	3100	0	0	Birth weight of baby 8 pounds, 10
9.83	---	130	88	8.0	--	--	--	90	3100	0	0	ounces
10.14	3.43	100	60	8.5	16	10	6	65	3160	0	0	Delivered Apr. 7, 1936
10.45	3.29	100	60	9.2	14	10	4	70	3190	0	0	Birth weight of baby 7 pounds, 13
8.11	3.39	---	--	---	--	--	--	--	----	0	0	ounces
10.61	4.86	---	--	7.8	--	--	--	--	3150	0	0	
9.98	3.35	90	60	7.8	16	11	5	85	3790	0	+	Delivered May 11, 1936
9.36	2.98	90	56	---	--	--	--	85	3800	0	+	Basal metabolic rate on Feb. 12, 1935
9.36	3.13	90	58	9.4	18	--	--	100	3810	0	0	+6%
10.14	---	100	52	8.0	18	--	--	105	3800	0	+	Birth weight of baby 7 pounds, 13½
11.90	4.04	105	68	7.0	18		--	90	3670	0	0	ounces
10.61	3.24	108	60	5.0	18	--	--	55	----	0	0	Delivered March 5, 1936
8.15	3.01	100	60	6.0	13	--	--	70	----	0	0	Basal metabolic rate on Nov. 25, 1935
10.92	3.51	90	60	5.1	--	--	--	80	----	0	+	−8%
12.17	3.99	110	70	7.5	--	--	--	70	----	0	0	Birth weight of baby 7 pounds
10.92	3.51	116	76	6.5	--	--		60	----	0	0	
9.67	3.82	104	60	10.0	16	8	8	60	3500	0	0	Delivered June 17, 1936
9.36	2.97	100	70	9.5	13			88	3620	0	+	Birth weight of baby 6 pounds, 9
9.83	3.23	106	76	7.3	14	--	--	95	3780	+	+	ounces
10.14	3.69	110	80	9.0	16	--	--	100	3850	+	0	
10.14	3.36	96	70	11.0	13	--		85	3700	0	0	
9.05	3.80	110	70	6.3	14	9	5	80	3150	0	0	Delivered June 10, 1936
9.05	3.55	110	60	6.2	13	9	4	85	3190	0	+	Birth weight of baby 6 pounds, 12
9.36	3.59	120	76	6.5	--			90	----	0	+	ounces
8.58	3.96	90	60	7.0	13	9	4	100	3190	+	+	
7.80	4.05	120	86	5.5	12	9	3	110	3240	+	+	
9.67	5.00	136	88	7.0	13	8	5	77	3030	0	0	
9.52	3.58	118	76	11.3	16	10	6	88	3370	0	+	Delivered June 5, 1936
10.30	3.52	118	64	9.8	17	--	--	95	3420	0	0	Birth weight of baby 9 pounds, 7
10.45	3.64	120	70	9.1	11	8	3	103	3120	+	0	ounces
10.45	3.63	110	70	8.7	11	10	1	115	3400	+	+	
10.30	3.86	108	62	9.0	15	11	4	85	3360	0	0	
8.74	2.74	96	60	10.0	--	--	--	70	---	0	0	Delivered June 23, 1936
10.30	3.02	100	56	7.0	--	--	--	70	3020	0	0	Birth weight of baby 8 pounds, 4
10.61	3.30	96	54	2.5	--	--	--	90	3070	0	0	ounces
12.01	4.07	96	68	4.5	--	--	--	75	2560	0	0	
10.45	3.79	100	58	5.1	--	--	--	85	2790	0	+	Delivered May 14, 1936
11.08	4.09	106	60	5.5	--	--	--	85	2810	0	+	Birth weight of baby 7 pounds, 13½
12.01	---	---	---	---	--	--	--	--	----	0	0	ounces
10.92	3.76	90	65	3.0	--	--	--	70	2710	0	0	
11.86	4.38	106	76	7.5	--	--	--	105	2660	+	+	Delivered Feb. 10, 1936
10.30	3.31	96	60	7.1	--	--	--	70	2600	0	0	Birth weight of baby 8 pounds, 1½ ounces
10.14	3.42	---	---	6.0	--	--	--	85	3300	0	0	Delivered June 24, 1936
10.61	3.40	110	58	5.5	--	--	--	100	3310	0	0	Birth weight of baby 7 pounds, 11¼
10.30	3.18	104	68	7.5	--	--	--	105	3280	0	0	ounces
10.14	3.00	96	60	9.5	--	--	--	110	3300	+	0	
12.17	4.38	120	76	8.5	--	--	--	75	3300	0	0	
9.52	3.18	100	60	7.5	--	--	--	90	----	0	+	Delivered March 23, 1936
12.01	4.64	100	60	8.5	--	--	--	70	----	0	0	Birth weight of baby 7 pounds, 4½ ounces
9.67	3.48	136	82	6.5	--	--	--	90	----	+	+	Delivered Feb. 26, 1936
10.30	3.72	120	82	7.5	--	--	--	85	----	0	+	Birth weight of baby 7 pounds, ¾
10.30	3.88	118	70	7.7	--	--	--	85	----	0	0	ounce
11.39	3.78	126	80	6.5	--	--	--	65	----	0	0	Delivered May 28, 1936
9.67	3.81	130	80	5.5	--	--	--	90	4050	0	0	Birth weight of baby 7 pounds, 2½
10.14	3.90	126	86	6.9	--	--	--	110	4190	+	+	ounces
10.76	4.42	118	80	6.5	--	--	--	80	4050	0	0	
9.98	4.04	120	80	8.0	--	--	--	95	4100	0	0	Twin pregnancy. Delivered March 3,
12.17	5.29	100	60	5.5	--	--	--	75	3800	0	0	1936
												Birth weights of babies 6 pounds, 15½ ounces and 6 pounds 10¾ ounces

Total Blood Volume.—Chart 2 shows the individual course of each patient's total blood volume and the average curve for the group.

The total blood volume varied between 4,070 and 6,830 c.c. ante partum, with an average value of 5,117 c.c., as compared with the range of a group of normal nonpregnant individuals of from 3,110 to 4,870 c.c., with an average of 3,920 c.c. It is significant that every ante-partum observation was above the average normal nonpregnant control value. The normal nonpregnant values, on the other hand, are closely approached by the post-partum range of from 3,140 to 4,720 c.c., an average of 3,987 c.c.

The curve of variation of the individual total blood volume did not in all patients, nor at every observation, parallel the curve of average values, although the same trend was unmistakable in most instances (Chart 2). This is also true of the plasma and cell volumes. There was a progressive increase in total blood volume to the ninth lunar month, at which time the average increase was 45.5 per cent above the average of the normal nonpregnant group (Chart 1, Table II). During the tenth month there was a definite diminution in total blood volume to 32.4 per cent above the normal nonpregnant level. There was a prompt return to normal nonpregnant limits by the second week post partum (Charts 1 and 2).

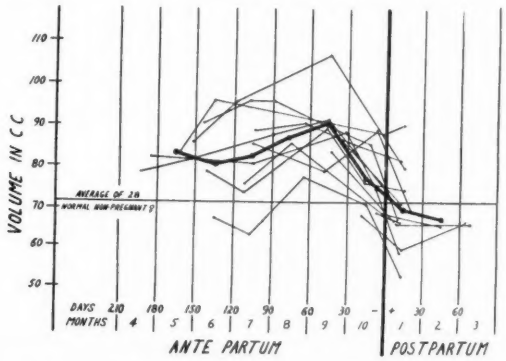

Chart 3.—The total blood volume in c.c. per kg. body weight in normal pregnant women. The fine connected lines represent the curves of individual patients; the heavy line the curve of average values. The heavy perpendicular line represents delivery and separates the ante- and post-partum periods. Note that on this basis of presenting the data the blood volume returns well toward "normal" during the tenth lunar month.

No obvious difference was noted in the curves of blood volume changes as between primiparas and multiparas.

It is of interest to note the total blood volume changes with respect to weight change in this group of patients. Accordingly, the total blood volume has been calculated in cubic centimeters per kg. of body weight (Tables I, II). Even on this basis the values during pregnancy in most instances are above those of the normal nonpregnant control group. The individual and average curves (Chart 3) are similar to those for the observed total blood volume. The maximum increase for total blood volume in terms of cubic centimeters per kg. of body weight is 25.2 per cent over the normal nonpregnant level. The predelivery decrease is considerably accentuated by this method of presenting the data, the decrease being from 25.2 per cent in the ninth lunar month to 7.7 per cent over the normal nonpregnant level in the tenth lunar month. The average values during pregnancy are all above the normal nonpregnant average of 71.7 c.c. per kg. of body weight, whereas the post-partum values are slightly below this figure (Table II).

For purposes of comparison, the course of the average total blood volume, total blood volume in cubic centimeters per kg. of body weight, plasma volume, plasma volume in cubic centimeters per kg. of body weight, cell volume, and the average hemoglobin, hematocrit and red blood cell count values are presented in Table II.

TABLE II

The average total blood volume, total blood volume in cubic centimeters per kg. body weight, plasma volume, plasma volume in cubic centimeters per kg. body weight, cell volume, hemoglobin, red blood cell count and hematocrit in normal pregnant women at varying intervals during pregnancy and the puerperium.

	DAYS ANTE PARTUM						DAYS POST PARTUM	
	151+	150-121	120-91	90-61	60-31	30-0	0-30	30+
Total blood volume in c.c.	4500	4715	4899	5405	5705	5190	3964	4052
Total blood volume in c.c. per kg. body weight	83.2	80.6	82.8	87.1	90.0	77.2	69.7	66.2
Plasma volume in c.c.	3186	3245	3332	3665	3913	3620	2507	2600
Plasma volume in c.c. per kg. body weight	58.5	57.5	56.3	59.2	61.7	52.8	44.2	41.8
Total cell volume in c.c.	1314	1452	1567	1740	1805	1681	1460	1452
Hemoglobin in grams	9.58	9.79	10.16	9.76	9.95	11.23	11.03	10.71
Red blood cell count in millions per c. mm. of blood	3.26	3.52	3.41	3.49	3.44	3.75	4.19	3.72
Hematocrit in per cent	30.53	31.02	32.07	31.98	31.34	32.43	36.80	35.21

Cell Volume.—It should be pointed out that in taking hematocrit readings no effort was made to read the level of packed red cells separate from the white cell and platelet layers, and our figures thus represent total blood cell volumes, though of course the red blood cells comprise the predominant part. Practically, the total cell volume may be considered the red cell volume in the absence of disease, involving either the platelet or white cell components of the blood.

The calculated cell volume of the blood varies during pregnancy. The changes observed, although relatively small, are similar in trend to those in the plasma and total blood volumes (Chart 1). Both the early pregnancy and the post-partum values average slightly below the nonpregnant average. During the ninth lunar month, when the cell volume increase is maximum, it amounts to 16.5 per cent over the average of the normal nonpregnant control group. It is evident then that there is actually an increase in the total number of red cells late in pregnancy (Chart 1). Despite this increase, however, a relative "anemia" (on basis of red blood cell and hemoglobin content per unit volume of blood) develops during pregnancy as a result of the failure of the cell volume to increase in the same proportion as the plasma volume (Chart 1).*

Red Blood Cells and Hemoglobin.—Analysis of the red blood cell counts and hemoglobin values, obtained from venous blood samples, shows a greater fluctuation between observations on the same individual, and a greater lack of absolute parallelism of the individual changes to the average changes for the group than that encountered in the blood volume determinations (Table I). This may be accounted for by actual individual variations in hematopoiesis and hemoglobin formation, or by the lesser accuracy of the methods used in their determination, or both. Again, the trend is nevertheless quite evident. In inverse relation to the plasma volume, the red cells and hemoglobin per unit volume of blood are below the average normal nonpregnant levels throughout pregnancy. During the tenth lunar month a return toward normal begins, which continues on through the puerperium. This predelivery increase in hemoglobin and hematocrit has been described before.[5, 11]

Simultaneous observations on *venous pressure* (arm), *circulation time* (arm to carotid, pulmonary and venous), *vital capacity, subcostal angle,* and *arterial blood pressure* are presented in Table I. The values of these functions are within "normal" limits and their behavior in this group of patients is similar to that of normal pregnant women described elsewhere.[4, 5]

*None of the patients in this series received any antianemic therapy.

Edema occurred in 8 of the 14 patients, usually during the last two months of pregnancy (Table I). *Dyspnea* occurred in 11 of the 14 cases. Neither bore any constant relationship to changes in the blood volume, although both edema and dyspnea were present, for the most part, late in pregnancy when the blood volume was usually at relatively high levels.

DISCUSSION

This study shows that there is an increase in the plasma, red cell and total blood volumes late, as compared to early in pregnancy, and an increase beginning early in pregnancy as compared to the nongravid state.

The average normal values, as determined in a control study in 28 normal nonpregnant women of an age group comparable to the series of cases herein studied, are 2,370 c.c. for plasma volume, 1,550 c.c. for cell volume and 3,920 c.c. for total blood volume. Gibson and Evans[10] have showed that the total blood volume of normal nonpregnant individuals bears a definite relationship to height. Based on their prediction values, the average of the total blood volumes of the 14 cases comprising this series in relation to height is 4,043 c.c., a value which compares favorably with the average total blood volume of 3,920 c.c. of the control group. This also corresponds well with the average values of 3,964 c.c. at two weeks post partum and 4,052 c.c. at later post-partum observations.

There are definite indications that a decrease in blood volume usually occurs in the last weeks of pregnancy, before the onset of labor. (Charts 1, 2, 3, Table I.) This correlates with observations from this clinic[5] and elsewhere,[11] showing a relative increase in the solid elements of the blood just before term. There is a marked post-partum decrease in the total blood and plasma volumes usually evident early in the puerperium. Since estimations of the blood loss at delivery are notoriously inaccurate they were omitted in this series. None of the patients, however, had excessive bleeding and can be presumed to have lost less than 500 c.c. of blood, an amount far less than the actual diminution in the total blood volume as between predelivery and postdelivery values which was found to average 1,226 c.c.

While for nonpregnant individuals the interpretation of blood volume values in terms of relation to body weight or surface area is of some comparative value, in pregnancy, this does not obtain for the weight is constantly changing due more or less to indeterminable and independent factors. The wide range of observation during pregnancy of 62.8 to 106.3 c.c. per kg. of body weight in this series demonstrates this contention.

While the blood is unquestionably more dilute during pregnancy than in the nongravid state, there are numerous evidences that the increased volume is not due to simple hydration. The formed and unformed solid elements of the blood decrease in concentration reciprocally with, but not in, the same degree as the increase in plasma volume. The mechanisms for blood cell formation and for the maintenance of the physicochemical balance of the blood apparently still

function as before pregnancy, although at a level too low to sustain the "normal" relationships. In the absence of nutritional deficiency in pregnancy it is emphasized, however, that the total solid constituents of the blood are equivalent to or are greater than the normal nonpregnant values.

Recently there have been specific studies of the water content of the blood during pregnancy, the results of which are in keeping with the results of this study. Feldman, Van Donk, Steenbock, and Schneiders,[12] made approximately monthly observations on 20 women during pregnancy on the hemoglobin, cell volume per cent, refractive index and water content of the blood. The water content reached a maximum at about 220 days' gestation, while the other values decreased up to the same point. Thereafter there was a tendency for these factors to remain unchanged until just before delivery, when there occurred a shift in the opposite direction. These authors concluded that the process of blood dilution is not an uncomplicated phenomenon because the reduction in protein content is far less than the reduction in total solids.

It is interesting that in a similar study on gravid lactating cows they found no significant blood changes which makes it likely that the dilution phenomenon is not concerned primarily with the physiology of lactation.

Oberst and Plass,[13] from average determinations on small groups of patients, nonpregnant, late in pregnancy, in early labor and seven to nine days post-partum, found a higher water content of the plasma and red cells with decreased specific gravity and plasma protein in the pregnant as compared with the nonpregnant. The cell volume and hemoglobin of the whole blood were decreased; whereas the hemoglobin content of the cells was increased. Early in labor the plasma and cells were slightly more concentrated, the specific gravity, proteins, cell volume and hemoglobin increased, while the water content decreased. After delivery the average values approached those of the nonpregnant group although the hematocrit and hemoglobin values remained increased and the water content of the cells and plasma decreased.

It is interesting to speculate on the cause of the increase in blood volume during pregnancy though by neither this study nor those in the literature has any causal factor been demonstrated. The teleologic argument that the maternal organism is thereby prepared for the blood loss of parturition may be coincidentally true, but offers no explanation whatever. It seems unlikely that the fetal respiratory exchange through the placenta benefits from a dilute maternal blood, although the fetal nutritional requirements may be more adequately met through an increased total blood volume. Neither purpose, however, provides a cause.

It has been suggested that the vascular sinusoids at the placental site are in effect an arteriovenous fistula.[14] Since an increased blood volume, and certain other circulatory changes which are observed in pregnancy, have been found in nonpregnant individuals with abnor-

mal arteriovenous communications, the alterations in the circulation in pregnancy produced by the placenta might be a contributory factor. One patient, Case 19 (Table I), who had a "normal" twin pregnancy had the largest total blood volume encountered so far in our studies on pregnant women. Although many other factors are probably operative under such circumstances, the large placental circulation required for a twin pregnancy is consistent with this hypothesis. It must be pointed out, however, that the "hydration" phenomenon with low hematocrit values and the diminution in the solid constituents of the blood are not usually found in nonpregnant patients with abnormal arteriovenous communications. Also, the predelivery decrease in blood volume demonstrated in this series is difficult to explain on such a basis, since the demonstrable morphologic changes, vascular degeneration and infarction, in the placenta and placental site are not of sufficient degree to account for the marked blood volume changes. From these considerations it does not seem likely that the behavior of the blood volume in pregnancy can be attributed solely to this mechanical factor.

That some hormonal influence may affect the blood volume changes observed in pregnant women is possible. In this respect one notes that in some diseases in which there are factors of glandular dysfunction present, such as hyperthyroidism, myxedema, and diabetes insipidus, there is an altered blood volume.

The increase observed in total blood volume early in pregnancy (in one normal patient not included in this series, on whom there were prepregnant data, a 5 per cent increase in total blood volume was present three weeks after conception, and a 12.5 per cent increase at seven weeks' gestation), before any significant mechanical factors are likely to operate suggests this possibility; also the predelivery reduction in blood volume which is not clearly related to altered circulatory channels in the placenta or other known factors. Evidence that water balance, which is disturbed in normal pregnancy, is under hormonal control is also suggestive. Recent work of Smith and Smith,[15] on serum prolan and estrin during the course of pregnancy is interesting, since the former shows a trend reciprocal to that observed in total blood volume. The endocrine and metabolic aspects of the problem require further investigation.

CONCLUSIONS

In normal pregnancy:

1. There is a progressive increase in the plasma and total blood volume beginning early in pregnancy which reaches a maximum during the ninth lunar month.

2. During the tenth lunar month there begins a definite decrease in both the plasma and total blood volumes which by the end of the second postpartum week brings them close to the average normal nonpregnant level.

3. There is a definite absolute increase in the total cell volume during the latter months of pregnancy, but one that is distinctly less in proportion than the increase in plasma volume.

4. The disproportionate increase in plasma volume appears to be primarily accountable for the phenomenon of "hydration" of the blood in pregnancy.

5. Factors which might contribute to the blood volume changes in pregnancy are discussed.

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PREGNANCY AND TUBERCULOSIS

A Study of End Results

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THE problem of the interrelationships between pregnancy and pulmonary tuberculosis is exceedingly complex, and notwithstanding the huge amount of work that has been done on the pathologic physiology of both conditions, we are still far from being able to answer many of the most fundamental questions. Why one woman takes a pregnancy or even repeated pregnancies "in her stride," so to speak, with but little apparent alteration in her bodily economy while her sister is brought to the very door of death by the same biologic process, is a question to which we can no more give a categorical answer today than we can to that of why one patient with a given tuberculous lesion in her lungs succeeds in healing the lesion without difficulty and enjoys perfect health for the remainder of her life, while another with the same type of lesion goes down hill and finally succumbs in spite of all therapeutic measures at present available. One is reminded of Osler's comparison of the evolution of tuberculosis in different individuals to the parable of the sower; the same comparison might almost be made with equal felicity to pregnancy. Given, then, two such variables, it is inevitable that they should react on one another in a variety of ways.

The history of the clinical attitude to the coexistence of the two conditions has undergone many modifications and changes, if not complete reversals. The Hippocratic view that pregnancy and parturition exerted a favorable influence on the course of phthisis was held until about the middle of the nineteenth century when the statistical studies of Louis and his contemporaries cast doubt on its veracity. The pendulum then swung to the opposite extreme, in spite of such excellent studies as those of Forssner, and it has been held until comparatively recent times that the influence of gestation on pulmonary tuberculosis was wholly bad and that every pregnancy in a tuberculous woman should be interrupted as soon as discovered. Just now we are in a more or less neutral phase with a tendency in most instances to sidestep the issue by saying that the cases should be individualized while advocating interruption in the majority. Certainly such extreme attitudes as that of DeLee, who holds that "until it can be incontestably proved that pregnancy actually improves the tuberculosis, this course (i.e., early interruption in every case of active tuberculosis) is most charitable," should be accorded but scant attention in the light of the experiences of such workers as Ornstein and Kovnat, Castlen, Schultze-Rhonhof and Hansen and many others. As a matter of fact, the question is in such a state of confusion at the present time that the burden of proof rests upon him who maintains that pregnancy does *not* exert a deleterious effect on pulmonary tuberculosis. One thus finds himself in the anomalous position of finding it necessary to prove that one condition does not have an adverse effect on another instead of advancing proof that it does.

Although an enormous literature has accumulated on the subject, very little real scientific data are available by which the interreactions between pregnancy and tuberculosis can be evaluated. This condition of affairs may be attributed to a number of factors of which the following may be mentioned: (1) the phthisiologist has but little interest in obstetrics and wishes to eliminate any condition that *may* interfere with his patient's recovery; (2) the obstetrician is seldom familiar with the natural history of pulmonary tuberculosis and is not in a position to follow the subsequent course of his patients for a sufficient time after delivery; (3) the practice of grouping under the head of "pregnancy" the three distinct, albeit closely related, functions of gestation, parturition, and the puerperium, each of which may exert an effect on the organism and hence on a pulmonary tuberculous lesion that is entirely distinct from the other two, has resulted in a confusion of data that are impossible to separate; and (4) as has been pointed out above, the reactions of individuals to tuberculosis and to pregnancy are so variable in themselves that an accurate prognosis for either condition is usually impossible at the initial examination.

The problem and the reasons for the inability to reach a decision on the influence of the two conditions on each other has been admirably set forth by Krause in an editorial which is recommended to all who are interested in the subject. "Merely a cursory examination of the customary treatise on the subject of tuberculosis and

pregnancy is sufficient to suggest, if not prove the solution,'' he says. ''Whether the individual inquiry approaches the problem biologically, statistically, clinically or, say, physiologically, it is at once apparent that, with few exceptions, the usual and average study proceeds from fallacious premises, gratuitous assumptions, and almost complete lack of definition and limitation of terms; and that from so unstable a foundation it limps through a morass of slip-shod data and the crudest handling of evidence to a palpably questionable conclusion. . . . Certainly it were anything but scientific to lay to *pregnancy,* in a woman who has tolerated her pregnancy extremely well, an activation or aggravation of her tuberculosis that followed an abnormal, exhausting or dangerous second stage of labor (as has frequently happened). . . . But, greater than any other fallacy in the customary approach to the problem of 'pregnancy and tuberculosis' is the almost universal premise and assumption that pregnancy acts as a 'constant' factor in whatever influence it may have on tuberculosis. That is to say, that all women tolerate pregnancy alike, which means nothing else than that the bodily economy of every woman reacts to pregnancy in the same way. Extensive reading would indicate that practically every author on the subject takes this most important datum for granted, notwithstanding its obvious falsity. Indeed, at the moment the writer cannot recall a study of 'tuberculosis and pregnancy' in which the author even casually suggested that pregnancy can act differently in different women or even differently in the same woman as one pregnancy follows another. . . . The most elementary practice soon teaches the observing physician that the bodily response of womankind to pregnancy is of almost 'infinite variety.' . . . And it would seem that any study or discussion concerning the influence of pregnancy on tuberculosis would have to take these facts into account. . . Even pseudoscience flies out the window when we are obliged to draw our conclusions from the data of ages lumped together, of non-discrimination between the variables of reproductive history of women undergoing observation and study, and so forth. . . . In summary, then, what are the known *facts?* They are, first, that pregnancy operates in widely divergent fashion on non-tuberculous women, that is, it may uplift and it may depress the individual economy; second, that pregnancy works to similar effect in tuberculous women, that is, it may rouse and it may quiet active tuberculosis. . . . Why, then, this pother and uncertainty? For any difference of opinion could be concerned only with what might be called quantitative effects, that is: Does pregnancy harm the tuberculous woman more frequently than it benefits her; and, if so, how much more? Before attempting to answer a problem, so insoluble on the basis of the data at hand, the writer begs permission to make a suggestion, as perhaps worthy of consideration in attempting a solution. He would put this in the form of a question, as follows: May it not be that pregnancy exerts a harmful effect on tuberculosis in those women who, without tuberculosis, would naturally tolerate pregnancy poorly, and a harmless or even beneficial effect on those tuberculous women who, without tuberculosis, would stand pregnancy well or even have their bodily economy improved by pregnancy?''

The present study was undertaken[1] to determine in what percentage of married women of childbearing age admitted to the Trudeau Sanatorium with active pulmonary tuberculosis the onset of the disease or its reactivation could be shown to bear a possible relation of a preceding pregnancy, and (2) to study the subsequent course of this group in comparison with a second group in similar age brackets manifesting pulmonary lesions of like extent. For this purpose the records of the Sanatorium from 1916 through 1935 (comprising approximately 5,000 admissions) were examined and the histories of the 457 married women between the ages of 20 and 35 (inclusive) set aside for study. In this group 6 cases were found to present incomplete data and were discarded, leaving a total of 451 cases for analysis.

The age group of 20 to 35 was chosen arbitrarily as covering the period of maximum childbearing. For the purposes of this study, pregnancies terminated either spontaneously or artificially in the first trimester (in most instances interruptions occurred in the first 8 to 10 weeks of gestation) were ignored as being unlikely to have an influence on either the onset or reactivation of the tuberculosis.

The 451 cases were divided into 6 categories as follows: (1) those who had had no viable pregnancies, (2) those who had had a full-term or viable pregnancy more than six months before the onset of the tuberculosis, (3) those who dated the onset of their tuberculosis from labor, (4) those who were pregnant when their tuberculosis was diagnosed but who continued to term, (5) those in whom a tuberculous process appeared within six months of the termination of a viable or full-term pregnancy, and (6) those who had become pregnant after the onset of tuberculosis. These groups, for the purposes of this study, may be combined under 3 large headings: (A) those who had had no viable pregnancies or a viable pregnancy more than six months before the onset of tuberculosis, who may be considered the controls, (B) those whose onset of tuberculosis bore some relation to a pregnancy, and (C) a small group who had been pregnant since tuberculosis had been diagnosed. The distribution of cases in each group, the extent of the disease on admission to the Sanatorium, and the mortality from tuberculosis in each group is shown in Table I.

TABLE I

	NO. OF CASES	PER CENT OF TOTAL	EXTENT OF DISEASE AND MORTALITY DUE TO TUBERCULOSIS IN EACH GROUP*					
			MIN.	DEAD %	M.A.	DEAD %	F.A.	DEAD %
No full-term or viable pregnancies	204	45.2	45	8.8	113	17.7	25	40.0
Full-term or viable pregnancy more than 6 months before onset of tuberculosis	159	35.2	29	10.3	97	17.5	19	57.9
Total controls	363	87.0	74	9.4	210	17.6	44	50.0
Full-term or viable pregnancy less than 6 months before onset of tuberculosis								
1. Onset tuberc. dated from pregnancy	22	4.8	3	0	18	16.6	0	0
2. Pregnant at onset of tuberculosis	16	3.5	5	0	9	33.3	2	100.0
3. No relation except time	16	3.5	0	0	9	11.1	5	40.0
Total	54	12.0	8	0	36	19.4	7	59.1
Pregnant since onset of tuberculosis	34	7.5	7	0	20	25.0	4	50.0

*Min., minimal; M.A., moderately advanced; F.A., far advanced.

The division of each group according to the extent of the pulmonary lesions on admission to the Sanatorium, using the classification of the National Tuberculosis Association, and the end results in each class are shown in Table II. Because of the small number of cases in certain of the subgroups, no attempt was made to express the mortality in percentages.

An analysis of the survival rates for five, ten, and fifteen years in each group is given in Table III. Here again percentages are omitted except in those groups

TABLE II

	MINIMAL				MODERATELY ADVANCED				FAR ADVANCED			
	ALIVE	DEAD OF TUBERCULOSIS	DEAD OF NONTUBERCULOSIS CAUSES	NO FOLLOW-UP	ALIVE	DEAD OF TUBERCULOSIS	DEAD OF NONTUBERCULOSIS CAUSES	NO FOLLOW-UP	ALIVE	DEAD OF TUBERCULOSIS	DEAD OF NONTUBERCULOUS CAUSES	NO FOLLOW-UP
No full-term or viable pregnancy	40	4	1	6	92	20	1	15	13	10	2	0
Pregnant more than 6 months before onset of tuberculosis	26	3	0	2	76	17	4	12	7	11	1	0
Onset of tuberculosis dated from full-term or viable pregnancy	3	0	0	0	15	3	0	0	0	0	0	1
Pregnant at onset of tuberculosis	5	0	0	0	6	3	0	0	0	2	0	0
No relation except a full-term or viable pregnancy within 6 months of onset of tuberculosis	0	0	0	1	7	1	1	1	3	2	0	0
Pregnant since onset of tuberculosis	7	0	0	2	15	5	0	1	2	2	0	0

TABLE III. SURVIVAL RATES

		5 YEARS			10 YEARS			15 YEARS		
		NO. CASES	SURVIVED	PER CENT	NO. CASES	SURVIVED	PER CENT	NO. CASES	SURVIVED	PER CENT
No full-term or viable pregnancies	Min.*	30	27	90.0	16	14	87.5	9	7	77.7
	M.A.	77	61	79.2	37	26	70.2	15	9	60.0
	F.A.	16	9	56.3	7	2	28.5	5	1	20.0
Pregnant more than 6 months before onset tuberculosis	Min.	18	17	94.4	8	6	75.0	8	5	62.5
	M.A.	74	63	85.1	47	35	74.5	21	9	42.4
	F.A.	15	7	46.6	9	2	22.2	5	0	0
Onset tuberculosis dated from full-term pregnancy or labor	Min.	2	2		1	1		0	0	
	M.A.	16	13	82.2	13	10	76.9	6	3	50.0
	F.A.	0	0		0	0		0	0	
Pregnant at onset of tuberculosis	Min.	4	4		2	2		1	1	
	M.A.	6	4		2	1		0	0	
	F.A.	2	0		2	0		1	0	
No relation noted except a pregnancy within 6 months of onset of tuberculosis	Min.	0	0		0	0		0	0	
	M.A.	5	4		5	4		5	4	
	F.A.	3	2		2	0		1	0	
Pregnant since onset of tuberculosis	Min.	5	5		2	2		2	2	
	M.A.	15	11	73.3	9	5	55.5	3	1	33.3
	F.A.	3	1		1	0		0	0	

*Min., minimal; M.A., moderately advanced; F.A., far advanced.

showing a sufficient number of cases to make such figures significant or indicative of trends. These data, under the two large headings of those patients who were nulliparas or whose pregnancy probably bore no relation to the onset of the tuberculosis and those in whom such a relationship might be shown to have existed, are summarized in Table IV.

Table V shows the type of onset in each group.

TABLE IV

		5 YEARS			10 YEARS			15 YEARS		
		NO. CASES	SURVIVED	PER CENT	NO. CASES	SURVIVED	PER CENT	NO. CASES	SURVIVED	PER CENT
Control Group	Min.*	48	44	91.6	24	20	83.3	17	12	70.6
	M.A.	151	122	82.1	84	61	72.6	36	18	50.0
	F.A.	31	16	51.6	16	4	25.0	10	1	10.0
Group with pregnancy relationship	Min.	6	6	100.0	3	3	100.0	1	1	
	M.A.	27	21	77.7	20	15	75.0	11	7	63.6
	F.A.	5	2	40.0	4	0	0	2	0	0

*Min., minimal; M.A., moderately advanced; F.A., far advanced.

TABLE V. TYPE OF ONSET OF TUBERCULOSIS

	PLEURITIC		INSIDIOUS		CATARRHAL		HEMOPTOIC		PNEUMONIC	
	NO. CASES	PER CENT	NO. CASES	PER CENT	NO. CASES	PER CENT	NO. CASES	PER CENT	NO. CASES	PER CENT
Pregnancy Group (54 Cases)										
Onset tuberculosis dated from pregnancy	1	4.5	13	59.0	4	18.1	4	18.1		
Pregnant at onset of tuberculosis	3	18.7	7	43.7	3	18.7	3	18.7		
Pregnancy within 6 months of onset of tuberculosis	3	18.7	6	37.5	5	31.2	1	6.2	1	6.2
Total	7	13.0	26	48.1	12	22.2	8	14.8	1	1.8
Control Group (350 Cases)										
No full-term or viable pregnancies	28	14.4	80	41.2	71	36.6	14	7.2	1	0.5
Full-term or viable pregnancy more than 6 months from onset of tuberculosis	24	15.3	64	41.0	57	36.5	11	7.0		
	52	14.8	144	41.1	128	36.5	25	7.2	1	0.2

While not pertinent to the purposes of this study, it is interesting to note that in this group the parity of the patient seemed to bear no relation to the extent of the pulmonary disease on admission to the Sanatorium. Specifically, of the 28 primiparas, there were 5 with minimal, 19 with moderately advanced, and 4 with far-advanced lesions. There were 4 deaths among the primiparas, of which 2 occurred in patients admitted with moderately advanced disease and 2 in patients classed as far advanced. Of 13 secondiparas, there were 2 minimals, 9 moderately advanced, and 2 far-advanced cases with 3 deaths: 2 in the moderately advanced group and 1 in the far advanced. Of 10 patients who had had more than 2 children on admission, there was 1 minimal, 8 moderately advanced, and 1 far-advanced case with 4 deaths, of which 3 occurred in women with moderately advanced lesions on admission and 1 in a patient with far-advanced disease.

In the patients who had become pregnant after the diagnosis of tuberculosis had been made there were 16 primiparas of which 5 had minimal, 8 moderately advanced, and 3 far-advanced lesions. In this group, 2 patients with moderately advanced and 2 with far-advanced cases died of tuberculosis. Of 12 secondiparas there were 2 minimals, 9 moderately advanced, and 1 far-advanced cases with 3 deaths in the group with moderately advanced lesions. And finally, 3 patients who had had more than 2 children were all classed as moderately advanced on admission and no deaths occurred in the group. Data obtained from the records on the health of the babies born of the pregnancies which appeared to be related to the onset of the tuberculosis are difficult to evaluate as the condition of the offspring was not given in 9 instances. Three babies are known to have died as follows: 1 stillbirth, 1 neonatal death on the second day, and 1 death from status lymphaticus at an unknown age. All the other children were noted as being in good health. Of the children born to patients after tuberculosis had been diagnosed, data on 2 were omitted from the records, 1 was recorded as being in "fair" health, 27 in good health, and 4 dead of the following causes: 1 neonatal death (this was the second child of this patient who had died within a few days of birth), 1 of malnutrition at 3½ years of age, 1 of meningococcic meningitis at 8 years of age, and 1 of unknown cause.

DISCUSSION

While it is only fair to point out that this study is based upon a selected group in that (1) only "favorable" cases are admitted to the Trudeau Sanatorium and (2) the cases came for the most part from an economic stratum financially able to receive treatment in a private sanatorium and, hence, a group which would be expected to carry out, at least in modified form, a proper regime for their tuberculosis on returning to their homes, it would appear that the end results are not materially affected by a preceding pregnancy. This, it would seem, is the important point to determine in attempting to evaluate the influence of a pregnancy on the end-results of a tuberculous lesion which it might have been a factor in aggravating. With such results in a group that has received adequate, or at least six months', treatment for tuberculosis is one justified in considering the group in whom the end results have not been so favorable, not because of a pregnancy, but because they failed to receive proper treatment for their tuberculosis? Any attempt to evaluate the influence of the physiologic functions of gestation, parturition and the puerperium on pulmonary tuberculosis which is not properly treated must be considered of dubious value as ample experience with the untreated disease shows a high mortality of itself.

Similarly, one must exclude as falling into the category of untreated or inadequately treated cases those whose economic conditions necessitate their leaving the sanatorium before the "cure" is complete to return to their homes and assume the burden of a household and a child. While the importance of this factor is not underestimated, it must be looked upon as a "side effect" of childbearing and not the act itself in considering its effect on tuberculosis. In other words, one must distinguish between the influence of *pregnancy*, and its accompanying labor and puerperium (for the three are divisible only in theory), and *childbearing* on pulmonary tuberculosis. This study would indicate that probably 12 per cent of *untreated* cases of latent tuber-

culosis in women of the childbearing age are reactivated or aggravated by gestation and its sequelae. Figures are not available by which this number can be compared with a similar group of *treated* cases; a limited personal experience, however, agrees with the findings of Alice Hill and others that reactivation or aggravation of properly treated cases occurs in a negligible proportion, especially when effective collapse therapy is instituted.

CONCLUSIONS

1. Of 451 married women between the ages of 20 and 35 inclusive who were admitted to the Trudeau Sanatorium between 1916 and 1935, approximately 12 per cent showed a possible relationship between the onset of their tuberculosis and a preceding viable pregnancy. In 3.5 per cent the symptoms first appeared during gestation and in 4.8 per cent the tuberculosis dated from parturition.

2. There is a slight tendency for the groups showing a relationship between the onset of the tuberculosis and pregnancy to exhibit more advanced types of lesions of admission to the Sanatorium. This does not, however, mean that the lesions manifested by this group tended to be more "acute" or show a higher incidence of exudative processes than those presented by the controls. While this finding may be interpreted as evidence of an unfavorable influence of pregnancy on a tuberculous process, it also suggests that with more careful examination of the lungs during the prenatal period many of these cases might have been diagnosed before symptoms appeared and proper *preventive* treatment instituted before the disease became activated.

3. There is no significant difference in the death rate from tuberculosis in the patients in whom the onset of the disease is related to a full-term or viable pregnancy as compared with that of a group of nulliparas of the same age group who show lesions of similar extent.

4. There is a relatively high incidence of hemoptoic onset of pulmonary tuberculosis in the group whose disease appears to bear a relationship to a gestation or parturition. While interesting in the light of the increased capillary permeability known to exist during pregnancy, the true significance of this observation is difficult to explain at the present time.

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THE EFFECT OF ESTROGENIC HORMONE UPON THE CONTRACTILITY OF THE FALLOPIAN TUBES*

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ALTHOUGH the hormonologic physiology of the uterine musculature has been the subject of intensive investigation by numerous workers, there is very little in the literature on the subject of the hormonal control of the Fallopian tubes. Because of certain clinical conditions related to tubal function (ectopic gestation and possibly, also, some forms of sterility and dysmenorrhea), it was felt desirable to determine the relationship of the Fallopian tubes to the various hormones which normally exercise a physiologic influence on the female gonads and genital tract.

The literature dealing with uterine musculature is extensive and the views held by different investigators are frequently contradictory (see Reynolds' review).[1] However, certain observations are generally agreed upon.

Athias[2] pointed out in 1919 that uterine motility is controlled by the ovaries. He demonstrated in guinea pigs that following castration, rhythmic spontaneous motility of the uterus is lost, but that motility could be restored in the ovariectomized animals by ovarian grafts. Similar views were held by Loewe[3] and Marshall.[4] Corner[5] gives Blair[6] credit for first reporting a relationship between uterine contractility and the estrus cycle. Blair noted that the contraction waves produced by a strip of uterine muscle immersed in Locke's solution varied at different points of the cycle. The rate was lowest at the time of estrus, increasing gradually to a maximum rate in the resting stage and decreasing at proestrus. Keye[7] working in Corner's laboratory confirmed and amplified the work of Blair. By means of "in vitro" experiments employing a segment of sow's uterus suspended in physiologic salt solution, he observed that when the strip of uterine muscle was taken from a sow killed during estrus, the contractions were large and slow. During the first few days following ovulation, the contractions became more rapid and less ample, and at the tenth day they were occurring at a rate of eight per minute. Similar changes in motility were established in a variety of laboratory animals, all having cyclic ovarian activity. Frank, Bonham and Gustavson[8] were able to demonstrate "in vitro," contractions characteristic of the estrus phase, in spayed rats which had previously been injected with estrogen extracts. Similar results (indicating that the estrogenic hormone will induce or augment uterine contractions) were obtained by numerous investigators.[9-16]

The fact that the ovaries control uterine motility in animals and that cyclic variations in this motility occur dependent upon the growth and development of the graafian follicle, was thus established by means of "in vitro" and "in vivo" experiments in animals.

*Presented at a meeting of the New York Obstetrical Society, October 12, 1937.

In human beings, Knaus[17] has demonstrated regular uterine contraction waves in normal cyclic females and that these contractions tended to disappear at the time when the corpus luteum was presumed to be at the height of its activity. Moir[18] obtained recordings of human uterine contractions by introducing into the uterus a small rubber bag connected with a Hurthle manometer. He found that the contractions were frequent, of small amplitude and regular during the first half of the menstrual cycle, but after the sixteenth day they became progressively stronger. Applying the technic of Moir to the puerperal uterus, Falls, Lackner and Krohn[19] demonstrated marked increase in uterine contractions following the administration of estrogenic hormone.*

That the Fallopian tubes are capable of muscular contractions was first pointed out by Kehrer.[20] He demonstrated kymographic recordings of contraction waves in isolated strips of excised tube. Seckinger[21] observed that the tubal contraction waves varied at different phases of the estrus cycle. He found two types of contraction waves, the first, consisting of a regular rhythm at the rate of four to six per minute, was present at all times of the cycle except for a few days before and after ovulation. During estrus, the rate became much more rapid (ten to fifteen per minute) with an alternation of groups of small and large excursions. Seckinger and Corner[22] observed somewhat similar variations in the contractions of segments of the Fallopian tubes of monkeys at different stages of the menstrual cycle. Wislocki and Guttmacher[23] were able to demonstrate tubal contractions by immersing the intact uterus and tubes of pigs in oxygenated Locke's solution.

Interest in the physiology of the Fallopian tubes was given a fresh impetus following the introduction of transuterine tubal insufflation by Rubin[24, 25] to determine the patency of the tubes. During the insufflation procedure, he observed that in patent tubes, variations occurred in the manometric pressure readings. Rubin subsequently demonstrated by means of kymographic recordings that these fluctuations were caused by tubal peristalsis. He furthermore established the fact that the contractions in normal unobstructed tubes produced a characteristic series of fluctuations on the kymograph. In women in the pre- and postclimacteric states, the tubal contractions were greatly diminished.

EXPERIMENTAL STUDY

We have undertaken to determine the effect exercised by the various hormones involved in the human cycle upon the motility of the Fallopian tubes. The problem of graphically recording tubal contractions was solved very simply by employing the transuterine tubal insufflation method of Rubin as it is used clinically in the study of sterility. Although the apparatus is primarily employed for the determination of patency of the Fallopian tubes, tubal contraction waves are automatically recorded in cases with normal unobstructed Fallopian tubes (Fig. 1). This method has the advantage of being performed with no risk and very little discomfort to the patient.

In the present investigation, it was planned to study the effect of an estrogenic principle of proved clinical efficacy upon the contractility of the Fallopian tubes. As experimental material, a group of women who were considered on clinical grounds to have very little or no ovarian activity was chosen from our Menopause Clinic. The women had all

*Since the completion of this paper, Krohn, Lackner, and Soskin (AM. J. OBST. & GYNEC. 34: 379, 1937) have reported the results of their studies on the effect of ovarian hormones on the nonpuerperal human uterus. To record uterine contractions they introduced a rubber balloon into the uterus and connected it to a recording device. They found that in normal patients the motility of the uterus varies at different periods of the menstrual cycle, the contractions being most marked in the first day of menstruation. Increase in the intensity and frequency of the contractions occurred following the administration of estrogenic substance, but after progesterone the motility was decreased.

ceased to menstruate and had symptoms characteristic of marked ovarian deficiency (hot flushes, weakness, headaches, and dizziness). It was felt that, if the ovarian estrogenic factor normally influenced tubal contractility, one would expect to find marked diminution in the tubal contractions in this group. Furthermore, if marked decrease in tubal contractility were proved in these cases, this group would constitute excellent experimental material upon which to test the ability of an estrogenic substance to restore normal tubal activity. The patients were insufflated and recordings made of the tubal contractions. They were then given a course of estrogenic hormone (estradiol-benzoate, progynon B)* injections and at the end of the period of treatment the insufflation was repeated, kymographic records being again made of the tubal contractions.

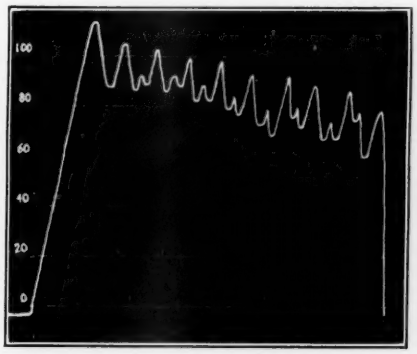

Fig. 1.—Normal tubal contractions in a woman with regular menstrual cycle.

In addition to the clinical evidence of ovarian deficiency, it was felt desirable to have some objective method of estimating the degree of estrogen deficiency and the response to the estrogen hormone. For this purpose the cytology of the vaginal secretions was studied in each case. Papanicolaou and Shorr[26-28] have shown that the human vaginal smear after the menopause exhibits certain well-defined cytologic characteristics indicative of ovarian deficiency, and that following the administration of adequate amounts of estrogen the smear resembles that of a female with normally functioning ovaries. Salmon and Frank[29] suggested a classification of the human smears into four groups to parallel the grading of rodent smears. In the present study, this classification was employed to indicate approximately the relative degrees of estrogen deficiency before treatment and the response to the injected estrogenic hormone.

EXPERIMENTAL PROCEDURE

Recording of Tubal Contractions.—The Rubin apparatus[30] was employed using the usual technic for insufflation. One hundred and fifty to 180 c.c. of carbon-

*We wish to express our thanks to Dr. Gregory Stragnell and Dr. Irwin Schwenk of the Schering Corporation of Bloomfield, New Jersey, for their kindness in supplying us with the progynon B employed in this study.

dioxide gas is introduced into the uterine cavity through a cannula which is connected with a mercury manometer and a kymograph. The pressure at which the gas enters the abdomen and the tubal contractions are recorded on the drum. In these patients, two or three preliminary recordings were taken, a week apart.

Estrogen Administration.—After the last preliminary insufflation, the patients were given a series of intramuscular injections of estradiol-benzoate in sesame oil (Progynon B—10,000 international units per c.c.). The total dosage varied from 120,000 to 650,000 international units given in divided doses over a period of ten to fourteen days at intervals of two to three days. After the last injection, a recording was made of the tubal contractions and repeated a week later.

Vaginal Smear Technic.—Vaginal smears were obtained by aspirating the surface secretion from the vaginal fornices with a glass pipette. The secretion was then diluted with saline and spread on a glass slide. The smear is then allowed to dry, stained with aqueous fuchsin for one minute, and washed with tap water. Vaginal smears were taken before the preliminary insufflation and twice weekly during the course of injections with progynon-B, and at the completion of the estrogen treatment.

Fig. 2.—Case 1. Preliminary insufflation showing few irregular weak contractions.

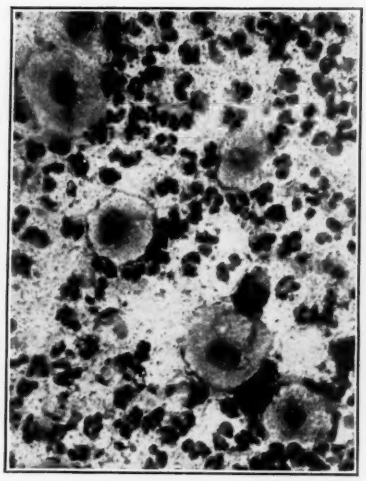

Fig. 3.

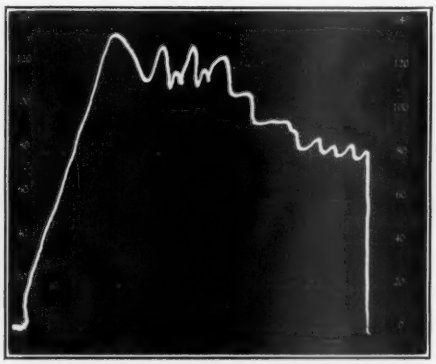

Fig. 4.

Fig. 3.—Case 1. Preliminary vaginal smear. Preponderance of leucocytes and "compact cells" indicative of estrogen deficiency. (Reaction I.)

Fig. 4.—Case 1. Tubal contractions after 190,000 I.U. of progynon-B. Note increased amplitude and frequency of contractions in contrast with preliminary recording (Fig. 2).

CASE HISTORIES

CASE 1.—In patient M. P., aged 48 years, a natural menopause occurred two years before this investigation. The preliminary insufflation was performed on June 27, 1936. The carbon dioxide passed through at a pressure of 25 mm. of mercury.

Irregular contraction waves of low amplitude were recorded (Fig. 2). The preliminary vaginal smear taken at this time exhibited a typical negative phase characterized by a preponderance of leucocytes with some scattered oval epithelial ("compact cells") cells containing large nuclei (Fig. 3). The patient was then given 190,000 international units of progynon-B during a period of two weeks. On the day following the last injection, insufflation was again performed (Fig. 4).

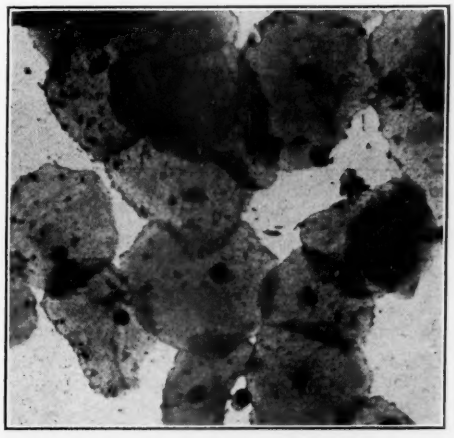

Fig. 5.—Case 1. Vaginal smear taken after estrogen therapy. Leucocytes and "compact cells" replaced by squamous epithelial cells, characteristic estrogenic effect. (Reaction IV.) Compare with preliminary smear (Fig. 3).

Fig. 6.—Case 2. Preliminary insufflation showing weak irregular contractions at low pressure.

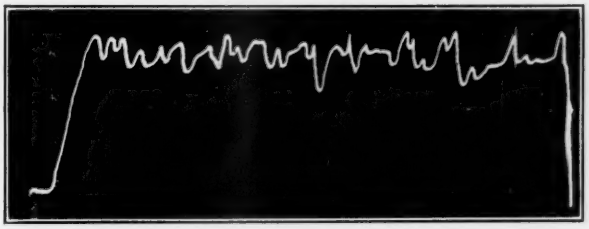

Fig. 7.—Case 2. Tubal contractions after 190,000 I.U. of progynon-B. Note frequent contraction waves of good amplitude at pressure of 55 to 70 mm. of mercury.

The pressure rose to 135 mm. of mercury and more or less regular contractions of moderate amplitude were recorded. A vaginal smear (Fig. 5) at this time exhibited a typical estrogenic effect characterized by the absence of leucocytes and "compact cells" and their replacement by large epithelial cells with small nuclei (Reaction IV).

CASE 2.—In this patient, I. G., aged 42 years, natural menopause occurred ten months before. The preliminary insufflation was performed on Feb. 1, 1936 with a maximum pressure of 50 mm. of mercury. After several weak initial contractions were recorded, the pressure dropped to 15 mm. of mercury (Fig. 6). The preliminary vaginal smear exhibited numerous nucleated oval cells and absence of cornified epithelial cells (Reaction II); 190,000 international units of progynon-B were then administered during eight days. Posttherapy insufflation was performed on the day of the last injection. Numerous contraction waves of good amplitude at a pressure of 55 to 70 mm. of mercury were recorded (Fig. 7). The vaginal smear at this time showed a complete estrogen effect. A third insufflation was performed seven days later. The contraction waves at this time were at low pressure (20 to 30 mm. of mercury), fewer in number, and irregular (Fig. 8).

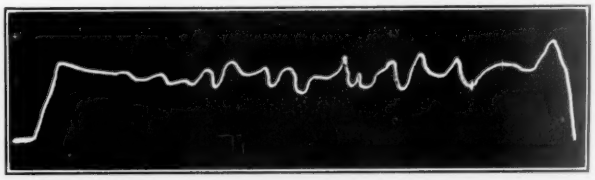

Fig. 8.—Case 2. Insufflation performed one week after cessation of therapy. Contractions are less regular, less frequent, and at reduced pressure.

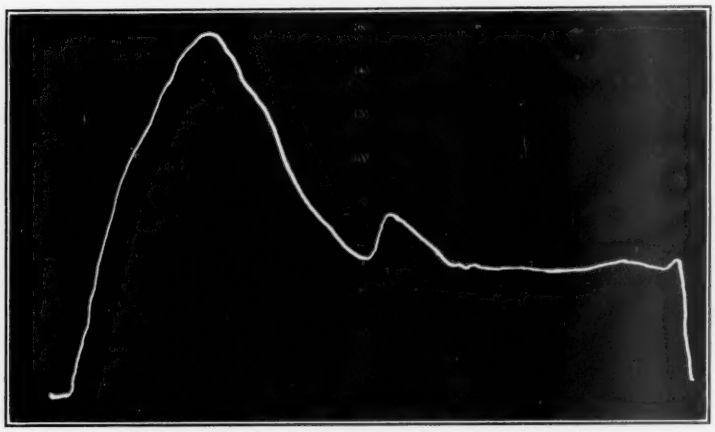

Fig. 9.—Case 4. Preliminary insufflation. No tubal contractions recorded.

CASE 3.—E. L., aged 52 years. X-ray castration was performed sixteen months before the present investigation. Four preliminary insufflations were performed at intervals of one week. In all, a few irregular contraction waves of low amplitude were recorded at the beginning. This was followed by a complete disappearance of fluctuations. The preliminary vaginal smear revealed a Reaction II, characteristic of estrogen deficiency. 190,000 international units of progynon-B were administered during seven days and insufflation was performed on the day of the last injection. The contraction waves recorded, though irregular, were of increased frequency and amplitude. The pressure however remained, for the most part, at a low level (20 to 40 mm. of mercury). The vaginal smear at the completion of the injections revealed a definite estrogen effect. Another insufflation was performed nine days later and revealed shallow, irregular contractions.

CASE 4.—M. S., aged 47 years, had a natural menopause of two years' duration. The preliminary insufflation on June 6, 1936 revealed an initial pressure rise to 160 mm. of mercury which became stabilized quickly at 55 mm. No contraction waves were recorded (Fig. 9). The preliminary vaginal smear contained leucocytes and compact cells (Reaction II). The patient was given 190,000 international units of progynon-B during the following nine days. Insufflation performed the day after the last injection revealed the following: the pressure rose to 115 mm. of

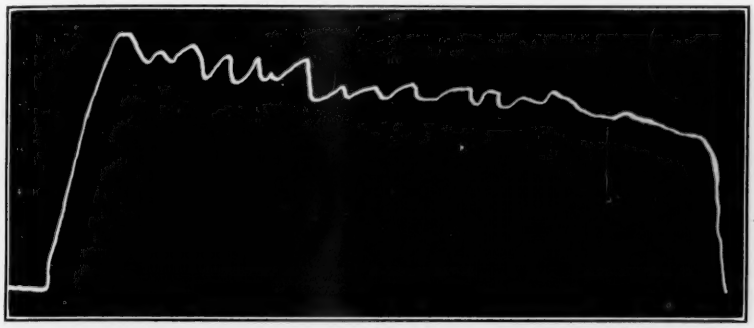

Fig. 10.—Case 4. Insufflation after 190,000 I.U. of progynon-B, showing numerous contraction waves at raised pressure level.

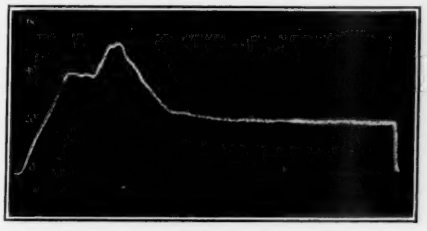

Fig. 11.

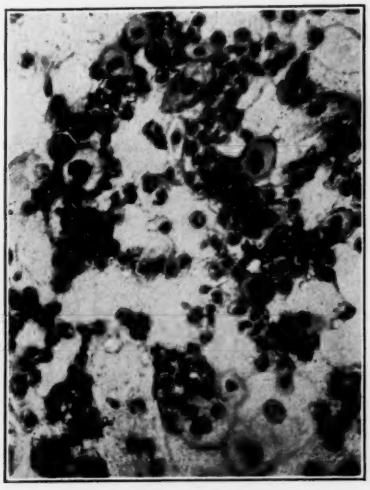

Fig. 12.

Fig. 11.—Case 5. Preliminary insufflation. Note total absence of tubal contractions.
Fig. 12.—Case 5. Preliminary vaginal smear. Predominance of leucocytes associated with numerous "compact cells" indicating marked estrogen deficiency. (Reaction I.)

mercury and more or less regular contraction waves were recorded at pressures varying between 80 and 110 mm. of mercury (Fig. 10). The posttherapy vaginal smear revealed a characteristic estrogen response.

CASE 5.—L. W., aged 51 years, had a natural menopause eleven years before. The preliminary insufflation was performed on March 6, 1937. The initial pressure rose to a maximum of 55 mm. of mercury and dropped quickly to 20 mm. of mercury with a total absence of contraction waves (Fig. 11). The vaginal smear exhibited a completely "negative" phase (Fig. 12) characterized by a predominance of

leucocytes together with numerous "compact cells." A total of 650,000 international units of progynon-B was given over a period of seven days. Posttherapy insufflation performed the day of the last injection revealed the following: the pressure rose to 95 mm. of mercury; regular contraction waves of high amplitude were recorded at pressures varying from 60 to 90 mm. of mercury (Fig. 13). The vaginal smear at this time showed full estrogen effect (Reaction IV) (Fig. 14). Insufflation was repeated sixteen days later. The pressure rose to a maximum of 35 mm. of mercury

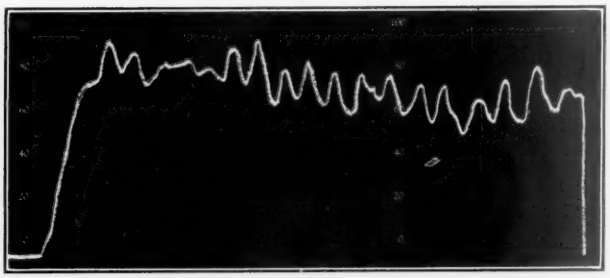

Fig. 13.—Case 5. Insufflation after 650,000 I.U. of progynon-B. Frequent, regular contraction waves of high amplitude at increased pressure. Compare with Fig. 11.

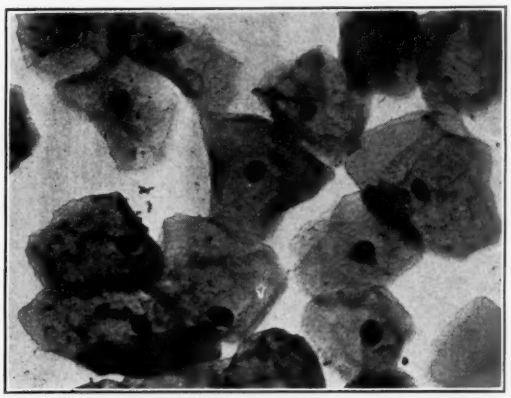

Fig. 14.—Case 5. Vaginal smear after 650,000 I.U. of progynon-B exhibiting strong estrogenic effect.

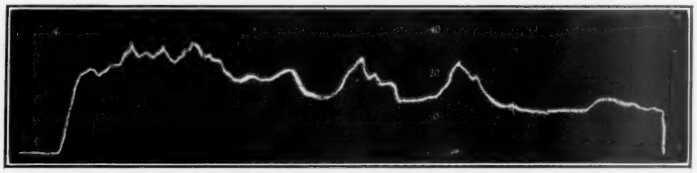

Fig. 15.—Case 5. Insufflation performed sixteen days after the last injection of estrogen. Contraction waves are irregular, of low amplitude, and recorded at low pressures (15 to 35 mm. of mercury). The effect of the injected estrogen has almost completely worn off.

and irregular contraction waves of low amplitude were recorded at pressures varying between 15 and 30 mm. of mercury (Fig. 15). The vaginal smear at this time still exhibited a moderate estrogen effect (Reaction III).

CASE 6.—C. H., aged 27 years. Menopause induced by x-ray four and one-half years before the present investigation. The preliminary insufflation was performed on April 4, 1936. The pressure rose to a maximum of 65 mm. of mercury. The

contraction waves were somewhat irregular but of fair amplitude. The preliminary vaginal smear revealed numerous epithelial cells of various sizes with occasional leucocytes and no cornified epithelial cells; 120,000 international units of progynon-B were administered during twelve days. The post-therapy insufflation was performed two days after the last injection and revealed regular contraction waves of good amplitude at a pressure of 45 to 60 mm. of mercury. The vaginal smear at this time exhibited full estrogenic effect. In this case, there was apparently some residual ovarian function in spite of the amenorrhea of four and one-half years' duration. This is indicated by the vaginal smear and accounts for the presence of tubal contraction waves in the pretreatment recording.

RESULTS

During the preliminary period, all cases showed definite diminution in tubal contractility. This was manifested by a total absence of contractions in some cases and in others by a markedly reduced amplitude as well as irregularity in the fluctuations. The recordings were also at low pressure. In most cases, after the introduction of the gas, several contraction waves were recorded which were irregular and of low amplitude. Thereafter, the contraction waves disappeared entirely. Apparently, the Fallopian tubes respond at first to the irritation caused by the gas with some weak, irregular contractions. The vaginal smears showed definite deficiency of estrogenic hormone in all the cases studied. In the older patients, those who were longest past the menopause, the smears exhibited the most regressive changes (leucocytes and compact cells) indicative of marked estrogen deficiency.

After the administration of the estrogenic hormone, increase in tubal contractility was noted. This was evidenced by the appearance of frequent, regular, rhythmic contraction waves of high amplitude at a heightened pressure level. Coincident with this striking change in the tubal motility, a definite change occurred in the vaginal smears, all of which exhibited characteristic estrogenic effects. It was noted that in the instances in which the smears exhibited the least regressive changes before treatment, the preliminary insufflation revealed some tubal contraction waves. This was interpreted as indicating that some estrogenic hormone was still being produced, even though the patient was no longer menstruating.

DISCUSSION

Although one would be inclined to assume from the observations made by numerous investigators on the subject of uterine contractility that the estrogenic hormone is responsible for the normal muscular contractions of the tubes, as well as the uterus, no direct experimental evidence had been submitted in support of such an idea. Rubin had observed diminished motility at the menopause and normal motility in some cases of prolonged amenorrhea. However, it must be conceded that clinical observations without parallel hormone studies are by themselves too inconsistent to permit of the formulation of a coordinated theory as to the relationship of ovarian function to tubal contractility.

In the cases studied in this investigation it was assumed on the basis of clinical criteria (amenorrhea, flushes, etc.), that the ovaries were

either not functioning at all or at a markedly reduced level. This was borne out by the vaginal smears which exhibited definite estrogen deficiency. In all of these cases there was striking evidence of marked decrease in tubal contractility as shown by the recording of few contraction waves of low amplitude or of none at all. Following the administration of the estradiol-benzoate, normal tubal peristalsis was restored as evidenced by the recording of regular, rhythmic contraction waves of high amplitude.

The striking change in the vaginal smears in each case which coincided with the return of tubal motility proves beyond question that the same hormonal factor, which is "estrogenic" (as shown by the vaginal reaction), will also initiate and maintain normal tubal peristalsis.

On the basis of these observations, the question arises as to whether tubal contractility may not be impaired in some patients whose ovarian function is subnormal. Furthermore, one must consider the possibility that such impairment of tubal motility may be the etiologic factor responsible for some types of sterility and tubal pregnancy.

SUMMARY AND CONCLUSIONS

1. It appears from this study that, after the menopause, with the gradual cessation of the production of estrogenic hormone, there is marked impairment of tone of the musculature of the Fallopian tubes and gradual disappearance of the regular rhythmic tubal peristalsis. This is demonstrated clearly in kymographic records by the reduced resistance to the entry of the gas and by the disappearance of regular rhythmic contraction waves. The most striking impairment of motility was observed in the cases longest after the menopause. In the recent cases, evidence of residual ovarian function was manifested by irregular contraction waves of low amplitude at low pressure.

2. Coincident with the impairment in tubal contractility, the vaginal smears exhibit signs of various degrees of estrogenic hormone deficiency. The most marked deficiency occurring in the patients showing least tubal activity.

3. Administration of estrogenic hormone in the form of the estradiol-benzoate (progynon-B) resulted in the development of rhythmic contraction waves of high amplitude, similar to those observed in normal females with functioning ovaries.

4. Coincident with the reappearance of tubal contractions, the vaginal smears showed full estrogen effects.

5. The striking restoration of regular tubal contractions in these cases parallel with the marked estrogenic effect manifested in the vaginal smears following the administration of the estradiol-benzoate indicates that in the human female the ovarian estrogenic hormone is responsible for the production of the normal rhythmic tubal contractions.

6. The possibility that impairment of tubal contractility due to estrogen deficiency may play a role in some forms of sterility and tubal pregnancy is suggested.

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THE NONPROTEIN, UREA, AND REST NITROGEN OF THE BLOOD DURING LABOR AND THE PUERPERIUM

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THE puerperium is a period of readjustment. The marked physiologic and anatomical changes which have occurred during pregnancy realign themselves at this time to normal nonpregnant conditions. It is necessary to know when and how these changes occur. Some take place immediately after delivery, others require days and sometimes weeks or even months before the truly normal nonpregnant conditions prevail.

In order to know whether the puerperium is actually following a normal course, it is necessary to know the normal limits. A great amount of work has been done on the chemistry of pregnancy and the puerperium but, as far as we can ascertain, no one has made a detailed study of the nonprotein and urea nitrogen of the blood during the puerperium.

In an earlier paper we presented our findings for normal pregnancy. They confirmed the work of other investigators, notably Williams, and Bunker and Mundell. We found that the nonprotein nitrogen decreases during the first six months of pregnancy from the average nonpregnant value of approximately 30, to 24 mg. per 100 c.c. of blood. During the last four months of pregnancy the nonprotein nitrogen

increases steadily to a value of 26 mg. at term and on the eighth day postpartum it averages 33 mg. per 100 c.c. of blood. The urea nitrogen diminishes during the first six months to a value of 6 mg. per 100 c.c. of blood and then maintains a constant level until the eighth or ninth month, when it begins to rise, having an average value of 7.2 mg. at term and 11 mg. per 100 c.c. of blood on the eighth day post partum.

We also pointed out that, due to the fact that the nonprotein nitrogen falls and rises more rapidly than the urea nitrogen, the rest nitrogen decreases during the first six months of pregnancy to a value of 18 mg. per 100 c.c. of blood and then increases during the latter part of pregnancy, being 19.2 mg. at term. It is further increased during the first week of the puerperium, reaching a value of 21.4 mg. on the eighth day post partum.

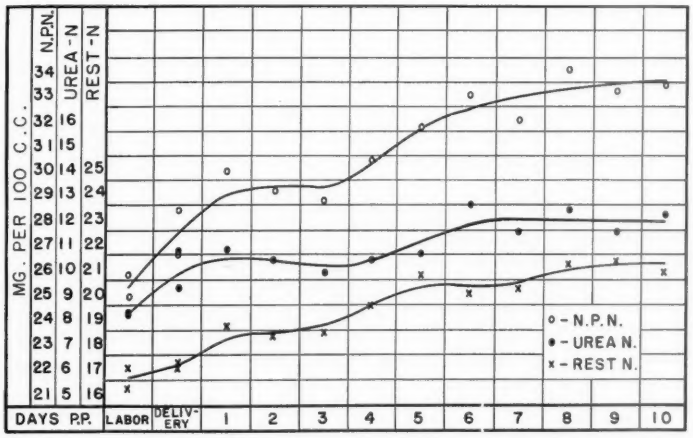

Fig. 1.—A graph illustrating the average values for nonprotein nitrogen, urea nitrogen and rest nitrogen of the blood during labor, immediately following delivery and during the first ten days of the puerperium.

At the time that paper was written, we had only a few analyses during labor and therefore did not emphasize our results. Now, however, we have made a study of 40 patients. Blood was obtained during the first stage of labor and immediately following delivery. These same patients also were studied during the puerperium. They were divided into two groups and blood was obtained from each group on alternating days; that is, from 20 patients, blood was drawn on the first, third, fifth, seventh, and ninth days post partum, while in the other group blood was drawn on the "even" days for ten days. The prime purpose for such a procedure was the comfort and convenience of the patients. It should be noted, however, that the curve in Fig. 1 has been drawn in respect to both groups, and therefore should be the same as that obtained if we had taken blood from each of the 40 patients every day.

METHODS

Filtrates prepared from whole blood by the procedures of Somogyi and Folin-Wu were used for the determination of urea nitrogen and nonprotein nitrogen, respectively. Urea nitrogen was determined by the manometric hypobromite method of Van

Slyke and Kugel. The method of Folin and Wu was used for the determination of nonprotein nitrogen. The rest nitrogen was calculated as the difference of the two.

By the term "rest" nitrogen we mean all the nonprotein nitrogen of the blood, excepting the urea nitrogen, in contradistinction to "undetermined" nitrogen which not only excludes urea nitrogen but also amino, uric acid, creatine, and creatinine nitrogen.

NONPROTEIN NITROGEN

According to Fig. 1 there is an increase during labor of approximately 2 mg. nonprotein nitrogen per 100 c.c. of blood, the average value during the first stage

TABLE I. NONPROTEIN NITROGEN

CASE	LABOR	AFTER DELIVERY	FIRST DAY	THIRD DAY	FIFTH DAY	SEVENTH DAY	NINTH DAY
1	31.6	28.0	34.1	23.6	29.4	28.7	32.6
2	26.0		29.4	30.6	31.6	31.1	34.3
3	27.1		28.6	30.4	26.0	35.5	40.0
4	24.6	21.9	30.2	29.2	30.2	31.6	33.5
5	23.2	28.8–		28.3	30.3	29.1	31.6
6	28.6	28.2	30.3	29.8	30.8	28.7	28.8
7	24.8	31.4	28.2	32.2	30.8		
8	19.7	25.1	24.7	25.3	30.8	26.2	27.4
9	24.2	48.0	48.8	33.7	29.8	31.1	39.7
10	23.9	23.1		27.4	30.2	30.2	34.7
11	27.8	24.7		26.3	35.7	40.2	42.9
12	26.2	28.8	29.1	25.5	33.7	38.7	37.5
13	21.8	24.9	27.8	30.9	31.9	33.3	33.3
14	33.7	36.0	33.1	35.1	36.2	34.7	35.3
15	28.0	27.6	29.2	32.4	34.3	32.8	32.8
16	26.1	29.4	25.6	28.7	27.9	36.0	30.9
17	23.0	30.6		24.7	34.5	30.2	32.6
18	24.2	25.9	30.6	30.3	25.1	34.3	31.4
19	35.1		30.6	33.3	41.9	33.7	34.3
20	25.1	26.7	26.7	29.7	31.9	33.3	27.4
Average	26.2	28.8	30.4	29.2	32.2	32.5	33.7

TABLE II. NONPROTEIN NITROGEN

CASE	LABOR	AFTER DELIVERY	SECOND DAY	FOURTH DAY	SIXTH DAY	EIGHTH DAY	TENTH DAY
21		29.4	32.6	28.0	33.5	36.4	33.7
22	35.6	24.4	30.2	33.0	37.3	34.9	38.0
23	23.1		25.6	29.6	33.1	33.1	33.3
24	21.8	23.9	30.4	30.8	33.3	34.5	33.7
25	22.3	24.6	24.8	33.3	37.7	33.1	34.5
26	25.6	26.2	26.1	26.1	32.2	34.9	40.2
27	21.9	27.9	26.7	26.8	33.7	32.2	27.9
28	24.0	25.3	30.9	28.2	29.8	31.7	29.6
29	26.2	37.3	29.4	27.0	32.2	31.7	32.8
30	22.9	25.1	26.9	26.0	29.1	26.2	29.6
31	24.7	22.1	26.7	28.8	36.0	35.7	35.3
32	29.6		30.9	40.5	34.7	38.0	36.4
33	20.8	24.3	34.9	37.3	39.7	40.5	36.4
34	27.4	27.2	33.9	34.9	34.9	32.2	33.0
35	28.4	30.8	29.6	37.7	34.1	42.9	37.0
36	23.5	28.2	30.2	37.3	32.4	41.1	36.4
37	26.2	29.2	24.9	31.9	30.9	34.5	41.6
38	33.0	34.3	40.8	30.3	37.3	32.1	27.8
39	24.2	23.1	26.4	25.9	32.2	32.6	30.6
40	19.8	22.3		24.2	26.9	31.6	30.6
Average	25.3	27.0	29.6	30.9	33.5	34.5	33.9

TABLE III. UREA NITROGEN

CASE	LABOR	AFTER DELIVERY	FIRST DAY	THIRD DAY	FIFTH DAY	SEVENTH DAY	NINTH DAY
1	8.7	8.9	9.7	8.1	9.9	9.6	8.7
2	8.8		11.4	13.0	11.8	9.1	12.4
3	7.1		8.7	10.4	10.4	13.5	12.3
4	12.0	7.5	10.3	9.3	8.4	10.1	10.1
5	9.0	10.5		11.2	10.4	11.0	10.2
6	9.9	13.7	13.9	10.3	9.3	9.7	8.5
7	7.0	11.3	9.8	9.9	10.2	11.7	
8	5.4	9.3	9.5	7.6	11.1	8.4	7.8
9	8.2	25.6	28.0	12.2	9.3	11.4	17.8
10	5.8	8.5		10.4	11.5	12.6	13.0
11	8.5	7.5		8.2	13.5	14.5	13.8
12	10.1	9.3	7.0	9.1	12.3	14.9	13.9
13	7.0	8.4	8.0	11.8	12.0	13.3	13.1
14	12.3	15.7	11.9	14.0	12.8	12.5	13.2
15	9.2	9.5	10.9	14.1	12.9	13.2	14.0
16	10.9	12.6	10.5	8.2	8.9	10.8	10.4
17	8.7	12.6		8.9	9.7	12.7	10.5
18	5.7	10.2	12.9	10.1	9.7	11.7	11.5
19	13.5		10.4	11.4	14.2	12.9	14.2
20	5.8	7.5	6.6	8.6	10.6	11.8	10.2
Average	8.7	11.1	11.2	10.3	11.0	11.8	11.9

TABLE IV. UREA NITROGEN

CASE	LABOR	AFTER DELIVERY	SECOND DAY	FOURTH DAY	SIXTH DAY	EIGHTH DAY	TENTH DAY
21		7.6	9.5	10.2	15.3	12.9	12.5
22	15.2	8.8	11.8	13.8	14.2	14.6	14.0
23	7.8		10.4	10.1	12.9	10.7	10.9
24	8.6	7.6	10.3	13.6	13.3	14.7	13.0
25	6.7	6.8	11.2	12.7	18.2	14.2	15.8
26	10.6	11.1	9.0	8.7	12.2	14.5	12.3
27	7.3	8.6	9.6	8.2	11.5	9.4	9.0
28	7.1	8.0	9.7	7.6	9.5	9.2	9.6
29	9.6	12.8	10.6	13.8	11.1	11.9	10.8
30	6.2	10.0	9.5	9.1	10.0	9.5	11.6
31	7.6	8.3	8.8	11.0	12.7	13.6	13.8
32	9.6		11.6	14.4	17.1	16.6	16.7
33	7.5	8.1	14.7	15.2	18.0	17.5	15.4
34	10.8	10.5	13.2	14.0	13.0	12.6	12.6
35	11.4	11.8	11.3	11.6	14.3	14.7	14.6
36	5.9	6.8	11.1	10.6	10.0	12.2	11.2
37	7.7	11.8	8.6	8.4	12.6	11.9	12.7
38	11.4	12.6	13.8	9.3	12.4	12.5	11.1
39	8.0	9.5	10.2	8.9	10.1	11.4	11.8
40	5.3	7.7		6.8	11.3	11.3	13.2
Average	8.6	9.5	10.8	10.9	13.0	12.8	12.6

of labor being 25.7 mg. and immediately after delivery 27.9 mg. per 100 c.c. of blood. Although this may seem as a very slight increase it may be noted that it is actually a rise of 8.6 per cent. Moreover a study of the individual cases in Tables I and II shows that only 8 of the entire series show an actual decrease, while all of the others either remain at approximately the same value or show a marked increase.

On the first day post-partum there is a further increase to an average value of 29.5 mg. This is followed by a period in which the curve levels off for about two days. From the third day until the tenth day the nonprotein nitrogen steadily increases until it has reached a value of 33.1 mg. per 100 c.c. of blood.

TABLE V. REST NITROGEN

CASE	LABOR	AFTER DELIVERY	FIRST DAY	THIRD DAY	FIFTH DAY	SEVENTH DAY	NINTH DAY
1	22.9	19.1	24.4	15.5	18.5	19.1	23.9
2	17.2		18.0	17.6	19.8	22.0	21.9
3	20.0		19.9	20.0	25.6	20.0	27.7
4	12.6	14.4	19.9	18.9	21.8	21.5	23.4
5	14.2	18.3		17.1	19.1	18.1	21.4
6	18.7	14.5	16.4	19.5	21.5	19.0	20.3
7	17.8	20.1	18.4	19.9	22.0	19.1	
8	14.3	15.8	15.2	17.7	19.7	17.9	19.6
9	16.0	22.4	20.8	21.5	20.5	19.7	21.9
10	18.1	14.6		17.0	18.7	18.6	21.7
11	19.3	17.2		18.1	22.2	25.7	29.1
12	16.1	19.5	22.1	16.4	21.4	23.8	23.6
13	14.8	16.5	19.8	19.1	19.9	20.0	20.2
14	21.4	20.7	21.2	21.1	23.4	22.2	22.1
15	18.8	18.1	18.3	18.3	21.4	19.6	18.8
16	15.2	16.8	15.1	20.5	19.0	25.2	20.5
17	14.3	18.0		15.8	24.8	17.5	22.1
18	18.5	15.7	17.7	20.2	15.4	22.6	19.9
19	21.6		20.2	21.9	27.2	20.8	20.1
20	19.3	19.2	20.1	21.1	21.3	21.5	17.2
Average	17.5	17.7	19.2	18.9	21.2	20.7	21.8

TABLE VI. REST NITROGEN

CASE	LABOR	AFTER DELIVERY	SECOND DAY	FOURTH DAY	SIXTH DAY	EIGHTH DAY	TENTH DAY
21		21.8	23.1	17.8	18.2	23.5	21.2
22	20.4	15.6	18.4	19.2	23.1	20.3	24.0
23	15.3		15.2	19.5	20.2	22.4	22.4
24	13.2	16.3	20.1	17.2	20.0	19.8	20.7
25	15.6	17.8	13.6	20.6	18.5	18.9	18.7
26	15.0	15.1	17.1	17.4	20.0	20.4	27.9
27	14.6	19.3	17.1	18.6	22.2	22.8	18.9
28	16.9	17.3	21.2	20.6	20.3	22.5	20.0
29	16.6	24.5	18.8	13.2	21.1	19.8	22.0
30	16.7	15.1	17.4	16.9	19.1	16.7	18.0
31	17.1	13.8	17.9	17.8	23.3	22.1	21.5
32	20.0		19.3	26.1	17.6	21.4	19.7
33	13.3	16.2	20.2	22.1	21.7	23.0	21.0
34	16.6	16.7	20.7	20.9	21.9	19.6	20.4
35	17.0	19.0	18.3	26.1	19.8	28.2	22.4
36	17.6	21.4	19.1	26.7	22.4	28.9	25.2
37	18.5	17.4	16.3	23.5	18.3	22.6	28.9
38	21.6	21.7	27.0	21.0	24.9	19.6	16.7
39	16.2	13.6	16.2	17.0	22.1	21.2	18.8
40	14.5	14.6		17.4	15.6	20.3	17.4
Average	16.7	17.5	18.8	20.0	20.5	21.7	21.3

Before going further it should be pointed out again that we believe that the smoothed curve is a better index of the true average than any individual point which represents an average of 20 cases. We shall therefore use the points intercepted by the curve as the average value for the 40 cases rather than the average obtained in each group of 20 cases.

UREA NITROGEN

During the first stage of labor we find the blood urea concentration to be 8.6 mg. per 100 c.c. of blood. Immediately following delivery we find that the average

value has been increased to 10.3 mg. This is an increase of 1.7 mg. per 100 c.c. of blood or in terms of percentage, 20 per cent. An inspection of Tables III and IV shows that in all of the cases excepting 5 there is either a very definite increase of the urea nitrogen concentration of the blood by the time of delivery or that it has remained the same as it was during the first stage of labor.

On the first day post partum there is a slight increase. This is followed by a leveling off or slight decrease for the next two days after which it increases to a level of about 12.4 mg. per 100 c.c. of blood, at which it remains from the sixth to the tenth day.

REST NITROGEN

There is a slight net increase in the concentration of rest nitrogen during labor. During the first stage of labor we find it to average 17.1 mg. per 100 c.c. of blood while immediately after delivery it is 17.6 mg. During the first day post partum there is a further increase followed by a fairly steady rise until the tenth day post partum, at which time the average value is 21.7 mg. per 100 c.c.

DISCUSSION

In our paper on the nonprotein, urea, and rest nitrogen of the blood during pregnancy we reported that on the eighth day post partum the average nonprotein nitrogen value was 33.1 mg. and the urea nitrogen value was 11.4 We had at that time only 15 cases, but in the present series of 40 cases we have obtained a figure of 33.7 mg. for the nonprotein nitrogen and 12.4 mg. for the urea nitrogen. The urea nitrogen figure for the present series is somewhat higher but the nonprotein nitrogen is practically identical.

Since there is a definite increase of the nonprotein nitrogen during the puerperium, it would be of interest to know what nitrogenous substances may be responsible for this rise. According to Fig. 1 the nonprotein nitrogen is increased during the puerperium from the initial values of 25.7 mg. obtained during the first stage of labor, to 34.0 mg. per 100 c.c. of blood on the tenth day post partum. This is a net increase of 8.3 mg. During this same period the urea nitrogen has increased from 8.6 mg. to 12.4 mg. a net increase of 3.7 mg. In other words 44.6 per cent of the increase of the nonprotein nitrogen can be accounted for by the increase of the urea nitrogen. Likewise the increase of the rest nitrogen is 4.6 mg. or 55.4 per cent of the increase of the nonprotein nitrogen.

In respect to this increase of the rest nitrogen we have also obtained the glutathione content of these bloods and the figures indicate that the increase of glutathione during the puerperium can account for 20 per cent of the rest nitrogen or 11.1 per cent of the nonprotein nitrogen. A résumé of the findings then shows that the increase of urea nitrogen accounts for 44.6 per cent, glutathione nitrogen 11.1 per cent, and the rest nitrogen (excluding the glutathione nitrogen) 43.3 per cent of the total increase of nonprotein nitrogen.

Although the literature has been searched, we have been unable to locate any publication in which a detailed study has been made of the

nonprotein and urea nitrogen during the puerperium. There are, however, some isolated values with which we can compare our figures.

For example Williams reports the average nonprotein nitrogen for the tenth day post partum as 33.6 mg. and the urea nitrogen as 12.9 mg. She also states that the average value for the nonprotein two or more months after confinement is 32.9 mg. with an urea nitrogen of 12.6 mg. In another report in which she confined herself to a study of the changes during labor she concluded that there is an appreciable rise in the blood urea and nonprotein nitrogen during labor in normal cases. She asserts that the urea nitrogen increases from 8.9 at the beginning of labor to 13.2 mg. per 100 c.c. of blood at the end of labor.

Caldwell and Lyle report the nonprotein nitrogen for primiparas as 26.7 and for multiparas as 29.4 mg. per 100 c.c. of blood at the end of delivery. The urea nitrogen for primiparas they report as 10.8 mg. while the average value for multiparas is 11.9 mg. Slemons and Morriss found the nonprotein nitrogen in 35 cases to average 25.2 mg. with the urea nitrogen averaging, for 12 cases, 10.5 mg. per cent at the time of delivery.

In comparing our figures with those of the above authors we find that the figures which Williams reports for the tenth day post partum are practically identical to ours. Those of Caldwell and Lyle are likewise of the same magnitude as those reported by us for the period immediately following delivery. The nonprotein nitrogen value reported by Slemons and Morriss is somewhat lower than our average, but on the other hand their average for blood urea nitrogen is similar to ours.

In our study of the changes during labor we confined ourselves to the net changes occurring between the first stage of labor and immediately after delivery. Siedentopf went one step further and made a detailed study of the changes of the nonprotein nitrogen during the various stages of labor. He divided labor into three parts as follows: Stage I, dilatation and the longest part of the second stage. Stage II, the last minutes of expulsion. Stage III, the third stage of labor. The investigation included only absolutely normal parturients who received no medicine or anesthesia of any kind. In Stage I a marked increase of nonprotein nitrogen took place in most of the cases. During Stage II the rise predominated. A decrease occurred in most of the cases during the placentral period. A very marked increased was noted again in the puerperium.

From this discussion one may conclude that the nonprotein and urea nitrogen of the blood is definitely increased during labor. According to Siedentopf there is not only a net increase of the nonprotein nitrogen during labor but there are marked changes during the various periods of this process. Furthermore the increase in the nonprotein and urea nitrogen which is initiated during labor continues during the puerperium until normal nonpregnant values are reached approximately by the tenth day. While we cannot state conclusively that the cause of the changes which we have observed is a process of dehydration of the blood, we believe that probably a concentration of the blood does play some part in these changes particularly those occurring during labor.

CONCLUSIONS

1. During labor the nonprotein nitrogen of the blood is increased from an average value of 25.7 mg. to 27.9 mg. per 100 c.c. of blood. This is an increase of 8.6 per cent.

2. During the puerperium there is a steady increase of the nonprotein nitrogen. On the tenth day the average value is 34.0 mg. per 100 c.c. of blood. The net increase is 8.3 mg. or in terms of percentage 32 per cent.

3. The blood urea nitrogen is increased during labor from an average value of 8.6 mg. during the first stage of labor to a value of 10.3 mg. per 100 c.c. of blood immediately following delivery, an increase of 20 per cent.

4. The concentration of the urea nitrogen is further increased during the puerperium. It attains a value of 12.4 mg. on the sixth day post partum and maintains this level until the tenth day. In other words, the concentration of blood urea has been increased 44 per cent during the puerperium.

5. The rest nitrogen of the blood increases only slightly during labor. The average for the first stage of labor is 17.1 and immediately following delivery 17.6 mg. per 100 c.c. of blood.

6. After steadily increasing during the puerperium, the rest nitrogen attains an average value of 21.7 mg. per 100 c.c. of blood on the tenth day post partum.

7. The increase of urea nitrogen accounts for 44.6 per cent, glutathione nitrogen 11.1 per cent, and rest nitrogen (excluding glutathione nitrogen) 43.3 per cent of the increase of 8.3 mg. of nonprotein nitrogen between the time of the first stage of labor and the tenth day of the puerperium.

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From the experimental data presented it seems that introduction of the male hormone into the blood stream of the female causes an upset in her sexual cycle. The ovaries are stimulated to a precocious and prolonged production of follicles which degenerate within the gland, with the result that no luteal tissue is formed.

Since none of these female mice developed mammary tumors, it seems reasonable to assume that proliferation and change to malignancy in the mammary glands may be due, in some measure, to the luteal fraction of the ovarian hormone.

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GYNECOLOGIC FEATURES OF CARCINOMA OF THE LARGE BOWEL

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THE gynecologist can usually determine with great accuracy the pathologic nature of any gross changes in the female generative organs after a routine abdominal and vaginal examination. In recent years his proficiency in clarifying organic changes has been greatly enhanced by the application of modern instrumental and x-ray methods for exploring the uterine cavity and its adnexa. Recent advances in endocrinology have also helped to recognize the nature of functional disorders of the female generative organs.

The experienced gynecologist has long recognized the fact that pathologic disorders in any organ in close proximity to the reproductive organs may simulate some primary disease in the uterus or adnexa and give rise to a confusing clinical picture. The senior author has seen two cases of regional ileitis operated upon for a suspected twisted ovarian cyst; in another patient a sacral kidney was mistaken for a fibroid; two other patients were operated upon for fibroids and found to have a lymphosarcoma of the small intestine. An appendicular abscess not infrequently presents clinical features resembling a tuboovarian abscess. Such errors are not at all uncommon.

We have observed several cases of carcinoma of the large bowel below the sigmoid simulating pathologic disorders of the uterus or adnexa. This paper is a brief report of 9 such instances found in a series of 125 cases of carcinoma of the colon and rectum, an incidence of 7.2 per cent. This study is in no sense a critical analysis but is designed to caution the gynecologist, and even the surgeon, that a carcinoma of the bowel particularly in the region between the sigmoid and the rectum, may simulate the clinical and physical features of uterine and adnexal disease.

A brief consideration of some of the pathologic features of carcinoma of the colon and rectum will help to appreciate the mode of production of certain clinical manifestations which lead to the interpretation that one is dealing with a gynecologic disorder.

The two most common types of carcinoma found in our series of cases are the infiltrating annular carcinoma which is more frequently found in the region between the upper ascending colon and the rectosigmoid junction, and the bulky cauliflower or polypoid type found more commonly in the cecum and the rectum. In the first type there is a great tendency to bowel obstruction, while in the second hemorrhage is a common feature. In both there is a pronounced tendency

to ulceration; this ulceration may be superficial or involve the entire wall particularly in the stenosing form. Secondary infection occurs and may play a prominent rôle in the sequence of pathologic events and clinical manifestations. Ulceration permits organisms to escape into and beyond the bowel wall and thus give rise to an acute inflammation of the bowel wall. If the infection passes beyond the confines of the bowel a large inflammatory mass may form.

In two-thirds of the cases analyzed, the location of the carcinoma was between the sigmoid and rectum. One can readily appreciate how a growth in the sigmoid or rectosigmoid which has a wide range of mobility because of a long mesentery, can gravitate into either fornix and be palpated on vaginal examination. To this mass the uterus or adnexa may become attached in an effort to prevent the spread of infection or even seal an impending perforation. This intimate association may be detected on vaginal examination and lead one to believe that either primary uterine or adnexal pathology exists. A localized abscess may develop, which may simulate a tuboovarian or pelvic abscess (Case 2). Perforation of the bowel into the free peritoneal cavity at the site of the carcinoma giving rise to a severe peritonitis has occurred several times in our series. Although this may not seem to be of interest to the gynecologist, nevertheless, the onset may suggest a pelvic peritonitis secondary to a tubal infection.

The following 9 cases of carcinoma of the bowel are reported very briefly.

CASE 1.—S. H., 60 years old, has been complaining for the past year of frequency of urination and dysuria associated with pain in the back and left lower quadrant. She had lost 45 pounds in weight. There was nothing else of significance in her history. On vaginal examination there was a mass about the size of an orange, in the left fornix which was also felt just above the left inguinal ligament; this mass was tender and not movable. Tubal infection was suspected. At operation an inoperable carcinoma of the sigmoid was found attached to the lateral pelvic wall. The abdomen was closed.

CASE 2.—D. N., 35 years old, had been operated upon elsewhere, five months before, for a pelvic abscess, which was drained through an abdominal incision. Following the operation she had been well until three weeks prior to admission, when she began to have cramps, marked constipation, and occasional vomiting; she had to resort to frequent enemas which lately were ineffectual. On examination, she was found distended; a small sinus was still present in her previous operative area. It was now believed that she had an intestinal obstruction secondary to a neoplasm in the large bowel, which had previously perforated and gave rise to a pelvic abscess. At operation a carcinoma of the sigmoid was found. A multiple stage Mickulicz operation was done. The pathologic report was a carcinoma. The patient was discharged after eight weeks. The gynecologist who had drained the pelvic abscess evidently overlooked the fact that a carcinoma of the bowel was present.

CASE 3.—P. K., 22 years old, complained of a sharp pain in the left lower quadrant radiating across the abdomen, which began twenty-four hours before admission. There was burning on urination and elevation of temperature. On abdominal examination, diffuse resistance was more pronounced in the left lower quadrant, where there was considerable tenderness. There was a suggestion of an ovoid mass in the left lower quadrant, more easily palpable in the left fornix on vaginal and rectal examination; this mass was quite tender. It was thought that this mass was a twisted ovarian cyst, although a left salpingitis or even an appendicular abscess

could not be definitely excluded. The surgeons concurred in this opinion. The sedimentation time was twenty minutes and gonococcus complement fixation was negative. The urine showed many pus cells and the blood a secondary anemia. At operation a carcinoma of the sigmoid was found with metastasis to the omentum and retroperitoneal lymph glands. The abdomen was drained because of the presence of a moderate amount of seropus; a culture of this turbid fluid was found negative and sections taken from the omentum showed adenocarcinoma. The postoperative course was stormy; she continued to have a septic temperature; she developed a fecal fistula and was discharged six weeks later in a very poor condition.

CASE 4.—J. H., 45 years old, complained of intermittent pains in the left lower quadrant for the past two years, accompanied by gaseous eructations. There was nothing significant in her past history except for loss in weight. On vaginal examination a hard tender mass was felt in the left fornix, which was thought to be an ovarian cyst, possibly malignant. Operation disclosed a large mass in the sigmoid, firmly adherent to a loop of small intestine. The sigmoid could not be mobilized and the abdomen was closed. Later on x-ray study of the large bowel revealed a carcinoma of the pelvic colon. Sixteen days after the first operation, the case was transferred to a surgeon who performed a cecostomy. Three weeks later a Mickulicz operation was done; she did poorly after the operation and notwithstanding supportive measures and a transfusion, she succumbed one week later.

CASE 5.—R. H., 48 years old, had a sense of pressure in the perineum, especially during defecation. During the past five weeks she had several attacks of mild diarrhea, but had not noticed the presence of blood. Her menstrual history was regular up to three months ago; last menstruation occurred five weeks prior to her admission to the hospital. Examination of the lungs revealed chronic fibroid phthisis. On vaginal examination there was felt a hard irregular mass in the cul-de-sac, the size of a hen's egg, slightly tender and somewhat fixed. On rectal examination this mass seemed to be situated in the rectovaginal septum and not encroaching on the rectal lumen. A tentative diagnosis of a tumor in the rectovaginal septum was made. Ovarian malignancy was considered a possibility. The urine and blood were normal; the stool showed the presence of blood. Proctoscopic study disclosed an ulcerating lesion below the rectosigmoid junction, sections of which showed an adenocarcinoma. Two weeks after admission the first stage of an abdominoperineal resection was done. A mass, the size of a fist, was found below the rectosigmoid adherent to the posterior wall of the uterus extending down to the cervix. The patient went into shock after the operation and died twenty hours later.

CASE 6.—E. B., 48 years old, complained of cramps in the lower abdomen for several weeks and constipation for several years; at times she noticed blood in the stool. On examination, the abdomen was moderately distended and not tender. On rectal examination, there was a small hard mass felt through the anterior rectal wall, which did not seem to involve the mucosa. A mass, the size of an egg, was felt in the cul-de-sac attached to the uterus; there was slight bleeding from the os. A tentative diagnosis of carcinoma of the body of the uterus was made although a lesion in the rectum was considered also possible. The urine showed a slight trace of albumin and the blood a moderate anemia. Proctoscopic and roentgen examination disclosed a carcinoma of the sigmoid with almost complete obstruction. A cecostomy was done and three weeks later a Mickulicz resection. The peritoneal fluid showed tumor cells. Two days after the operation, she died of peritonitis.

CASE 7.—E. R., 49 years old, had cramplike pain in the lower abdomen for the past few years, which became aggravated on walking. She has been constipated for many years and in the past year she lost 30 pounds in weight. Six months before she was admitted to the hospital, x-rays of the gastrointestinal tract failed to show any lesion. Her menses were regular until three months ago and since then she had had only one period. The patient appeared cachectic. On vaginal examination, a hard nodular mass was felt in the cul-de-sac; this mass was not tender and seemed fixed to the surrounding structure; the uterus was enlarged. The clinical impression was that she had a carcinoma of the body of the uterus. At op-

eration a carcinoma of the rectosigmoid junction was found adherent to the uterus and pelvis. It was considered inoperable; the abdomen was closed and the patient discharged two weeks later.

CASE 8.—Patient, 38 years of age, complained of abdominal cramps for the past two years, which had no relation to meals. There were no other symptoms. On vaginal examination a hard mass was found attached to the uterus and was thought to be a fibroid. At operation a carcinoma of the rectosigmoid was found adherent to the bladder and uterus. The mass was easily separated, permitting the first stage of a Mickulicz resection. The subsequent steps were completed by the surgical staff and the patient was discharged ten weeks after the first operation. Pathologic study disclosed an adenocarcinoma of the rectosigmoid with lymph gland metastasis.

CASE 9.—M. R., 25 years old, complained of pain in the left lower quadrant for the past month. This pain appeared suddenly and radiated to the back. A slight diarrhea and frequency of urination accompanied the onset of this pain. Examination of the abdomen revealed a palpable sigmoid colon. On vaginal examination the uterus felt normal. A mass was felt in the left fornix, the size of a hen's egg; it was fixed and slightly tender. This mass could also be felt on rectal palpation although the rectal mucosa seemed free. The opinion was that this mass was inflammatory, although carcinoma of the ovary was also considered likely. A junior member of the gynecologic staff advised study of the colon and rectum because he could not exclude a lesion of the bowel. At operation, a rectosigmoid carcinoma was found. A surgeon was immediately available to perform the first stage of an abdominoperineal resection. A diagnosis of carcinoma was confirmed by the pathologist. Eleven days later the second stage was completed and the patient died of shock several hours later.

These cases are reported to illustrate how a lesion such as a carcinoma of the bowel can simulate a gynecologic disorder and justify to a certain extent the clinical errors committed not only by the gynecologist but the surgeon as well. We do feel, however, that a very careful evaluation of symptoms and findings should help one to avoid such pitfalls in diagnosis. In the many cases that come to the gynecologist with some lesion of the generative organs, the task of recognizing the pathologic nature of the disorder is comparatively simple because of the definite characteristic features presented by a fibroid, ovarian cyst or tubal condition; usually the clinical diagnosis is confirmed at operation. It is always well to suspect a neoplasm in the colon when a mass is found on vaginal examination which does not conform to the characteristics of either one of the above lesions, particularly if there are symptoms referable to the large bowel. We do not advocate the indiscriminate use of the x-ray or the proctoscope in those cases where a gynecologic disorder is clearly established; nevertheless, in the more obscure cases with an undefined pelvic mass the application of these necessary diagnostic procedures will not only help clarify the origin of a pelvic mass but also reduce the incidence of error.

In Case 9, there were symptoms referable to the large bowel and barium enema was suggested to determine if the mass had any connection with the colon. In Cases 5 and 6, a gynecologic lesion was believed to exist but because of the unusual features of the palpable mass, proctologic examination was made and disclosed the mass to be a carcinoma in the bowel.

In routine practice, when the gynecologist mistakes a fibroid for an ovarian cyst or hydrosalpinx, it is of no great importance. The patient's postoperative course is not affected by this clinical error. When, however, he finds an unsuspected carcinoma of the colon, the consequences of such error may have serious sequelae. The preparation for the routine gynecologic operation is not very important, whereas the prognosis in patients to be operated upon for carcinoma of the large bowel depends very much on proper preoperative preparation of the patient. Any attempt at radical removal of the growth even by a competent gynecologist or surgeon when the patient is not properly prepared for it is to be avoided.

The problem arises as to the mode of procedure in the event that the lesion is unexpectedly found at operation. To the gynecologist who is an experienced abdominal surgeon, there will be no difficulty in proceeding along accepted surgical lines. If his surgical experience is limited to the reproductive organs, he will undoubtedly content himself with closing the abdomen and transferring the patient to a surgeon or even feel that the case is inoperable. We strongly recommend, under such conditions, a preliminary cecostomy which is easily performed and might even shorten the surgical period. The major operation can then be deferred to the surgeon. The diversion of the fecal stream is particularly advantageous when either a partial or complete obstruction is present. Cecostomy decompresses the bowel and more thoroughly prepares the patient for the subsequent surgical procedures. Not infrequently a carcinoma of the bowel, because of the associated ulceration and infection, will give rise to a mass largely consisting of inflammatory reaction. This might give the erroneous impression at the time of exploration that an inoperable lesion exists, as was the case in Patients 1 and 7. It is surprising how this inflammatory reaction will subside and the mass diminish greatly in size after the fecal current is diverted by means of a cecostomy. What was first considered to be an apparently inoperable growth becomes more readily resectable. If an abscess is present as in Case 2, simple drainage should suffice for the time being, because any attempt at more radical surgery at this time would jeopardize the patient's chance for recovery.

It is needless to state that the mere invasion of the uterus or adnexa or their attachment to the mass does not preclude a radical extirpation of the bowel. The removal of the uterus with its adnexa along with the colon neoplasm is not a difficult procedure and should not discourage the surgeon.

SUMMARY

Several cases of carcinoma of the large bowel are reported which because of their clinical features were erroneously diagnosed as suffering from a gynecologic disorder.

We believe that a more careful evaluation of the clinical findings and history, and the application of the proper diagnostic procedures,

in some of the patients who present an obscure pelvic mass, will undoubtedly help to eliminate such errors.

In cases of such mistaken diagnosis, the gynecologist should bear in mind that a cecostomy is a preparatory and most valuable step in the surgical management of the cases.

If at operation a pelvic abscess is found whose origin seems uncertain, one should determine subsequent to surgical drainage, if there is any possible connection to a growth in the large bowel.

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PITOCIN IN THE THIRD STAGE OF LABOR

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THE effect of pitocin on the duration of the third stage of labor was observed in 630 patients. The blood loss incident to the separation and delivery of the placenta was determined in each case. The observations included blood pressure changes and systemic manifestations following the intravenous and intramuscular injection of pitocin. The undesirable pressor effect of pitressin and pituitrin as well as the danger of an allergic reaction was avoided by the use of pitocin.

METHOD

An oxytocic was administered routinely at the beginning of the third stage to a series of patients with normal and abnormal pregnancies. This series included operative as well as spontaneous deliveries. Pitocin was administered intravenously, except in a few cases in which difficulty was experienced in passing the needle into the vein, then it was given intramuscularly. In a few instances pituitrin was given intramuscularly, but never intravenously. Ergotrate was also given intramuscularly in a few cases. The blood pressure was taken routinely during the first and second stages of labor and repeated three minutes after the injection. The patient's arm was prepared during the second stage for the intravenous injection to avoid any delay at the onset of the third stage. After aspirating 2 to 3 c.c. of blood to dilute the pitocin, the mixture was injected slowly over a period of one minute. During the third stage the blood was collected in a basin held against the perineum. Expulsion of the placenta from the lower uterine segment and the upper part of the vagina was done routinely as soon as the separation of the placenta was completed. In each case the amount of blood loss on drapes and sponges was estimated. No attempt was made to exclude blood loss from episiotomy wounds or cervical and vaginal lacerations. The collected blood was not infrequently contaminated with amniotic fluid. The hemoglobin was determined just before delivery and again on the tenth day of the puerperium.

In the present series of 630 patients, 505 received 0.5 c.c. of pitocin intravenously immediately following the delivery of the baby, and 125 patients received 0.5 to 1.0 c.c. of pituitrin or pitocin intramuscularly. In each instance the total blood loss was recorded, which equals the measured blood collected in the placenta basin plus the estimated blood loss on drapes and sponges.

RESULTS

The patients, who received intravenous pitocin, had an average blood loss of 171.0 c.c., a measured blood loss of 66.5 c.c., and an estimated blood loss of 104.5 c.c. In the comparison those patients, who received an oxytocic intramuscularly, had an average total blood loss of 203.9 c.c., a measured blood loss of 83.3 c.c., and an estimated blood loss of 120.6 c.c. Of those patients who received intravenous pitocin, 50.0 per cent had a total blood loss of less than 150 c.c., and 89.1 per cent had a measured blood loss of less than 150.0 c.c. Of those who received an oxytocic intramuscularly, only 28.0 per cent had a total blood loss of less than 150.0 c.c., and 72 per cent had a measured blood loss of less than this amount. The foregoing figures indicate a definite advantage in the use of intravenous pitocin over the intramuscular injection. Tables I and II and the curves in Fig. 1 show that among those patients who lost less than 150 c.c. of blood, there was a higher percentage of those who received intravenous pitocin than there was of those who received an oxytocic intramuscularly.

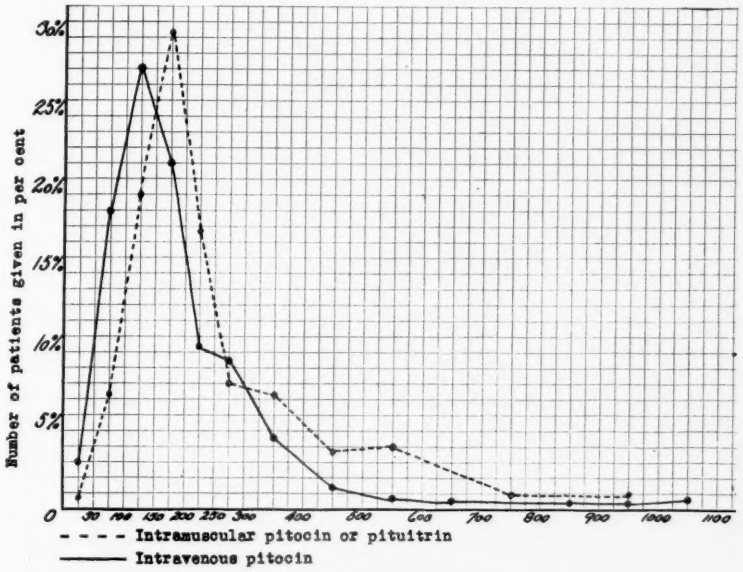

Fig. 1.—The blood loss is shown in cubic centimeters. The number of patients in each group is expressed in percentage. The curves show that of the patients who received intravenous pitocin a larger percentage lost less than 150 c.c. of blood than was the case with those patients who received intramuscular pitocin or pituitrin.

The average duration of the third stage was 5.4 minutes with the intravenous pitocin and 6.5 minutes with the intramuscular oxytocic. In the group of patients receiving intravenous pitocin, the delivery of the placenta was frequently completed before all the pitocin had been injected into the arm vein. Retention of the placenta requiring manual removal occurred only twice in the entire group of patients, and in both the cervix was found to be open.

On the tenth day of the puerperium the average hemoglobin reading of those patients who received intravenous pitocin was 4.3 per cent higher than that of the patients who received intramuscular pitocin or pituitrin.

DISCUSSION

Pitocin has been selected as the oxytocic in this study for the following reasons: (a) it produces no appreciable change in blood pressure, except when traces of the pressor principle are present; (b) this oxytocic is

TABLE I. DATA OF PATIENTS GIVEN INTRAVENOUS PITOCIN

The Distribution of Blood Loss Among 505 Patients Who Received Intravenous Pitocin at the Beginning of the Third Stage of Labor

BLOOD LOSS C.C.	NO. PATIENTS TOTAL BLOOD LOSS	NO. PATIENTS MEASURED BLOOD LOSS	NO. PATIENTS ESTIMATED BLOOD LOSS	PER CENT OF PATIENTS WITH TOTAL BLOOD LOSS
1000	2	1		0.4
900-1000	1			0.2
800- 900	1			0.2
700- 800				
600- 700	3		1	0.6
500- 600	3	3	3	0.6
400- 500	6	1		1.2
300- 400	24	4	8	4.5
250- 300	48	3	7	9.6
200- 250	54	10	31	10.4
150- 200	110	33	53	22.0
100- 150	143	97	145	28.0
50- 100	95	169	200	19.0
0- 50	15	184	57	3.0

TABLE II. DATA OF PATIENTS GIVEN INTRAMUSCULAR PITOCIN OR PITUITRIN

The Distribution of Blood Loss Among 125 Patients Who Received Intramuscular Pitocin or Pituitrin at the Beginning of the Third Stage of Labor

BLOOD LOSS C.C.	NO. PATIENTS TOTAL BLOOD LOSS	NO. PATIENTS MEASURED BLOOD LOSS	NO. PATIENTS ESTIMATED BLOOD LOSS	PER CENT OF PATIENTS WITH TOTAL BLOOD LOSS
1000				
900-1000	1			0.8
800- 900				
700- 800	1			0.8
600- 700				
500- 600	5	3	1	4.0
400- 500	4		2	3.6
300- 400	9	1	6	7.2
250- 300	10		5	8.0
200- 250	22	14	6	17.6
150- 200	38	17	10	30.4
100- 150	25	21	35	20.0
50- 100	9	42	52	7.2
0- 50	1	27	8	0.8

a nonprotein which does not subject the patient to the dangers of an allergic reaction; (c) the use of intravenous pitocin in unanesthetized patients indicated that this oxytocic does not produce any deleterious effect; (d) its use is not contraindicated in patients with toxemias of pregnancy, chronic nephritis, or arterial hypertension; (e) it produces a contraction of the uterus within one minute following the intravenous administration; (f) there is evidence that this principle will yield more satisfactory and uniform oxytocic results when administered by itself, than when mixed with the pressor hormone (Kamm[1]).

While pituitrin is commonly used in repeated doses to control hemorrhage after the delivery of the placenta, the indiscriminate use of this hormone is to be deprecated because of the constrictor effect on the

peripheral circulation and the depressor effect on the heart. For these reasons pituitrin is contraindicated in arterial hypertension, chronic myocarditis, and the toxemias of pregnancy.

Pastore[2] has reported one fatality, which may have been due to the intravenous use of pituitrin. Simon[3] has reported a case with specific hypersensitiveness to pituitary extract, in which there was no personal or family history of allergy and with negative tests to the common allergens. In this patient pitressin gave a positive test and pitocin gave a negative allergic reaction. Schockaert[4] reported a woman with a normal obstetric course, in whom eclamptic-form convulsions developed following the injection of pituitrin, and concluded that this manifestation was due to the vasopressor component. Dieckmann and others[5] have indicated that the use of pituitrin is contraindicated in pre-eclamptic patients, whereas pitocin does not produce any undesirable effects in the toxemic patient.

Shock was noted in only one case in the series of 630 patients. This occurred in a patient with a toxemia, who had received intravenous pitocin. Signs of circulatory collapse did not develop until one hour after delivery.

This patient had previously lost six premature babies. She was admitted to the hospital at the end of the seventh month of gestation, because of albuminuria and a blood pressure of 180/136. She was under observation for a period of four weeks and then labor was induced by the insertion of a bougie. The labor was of six hours' duration and the delivery was spontaneous, with a blood loss of 415 c.c. Her hemoglobin reading prior to delivery was 62 per cent. Following transfusion and supportive treatment the patient made a satisfactory recovery, although she continued to have hypertension and albuminuria. In order to determine whether or not the intravenous pitocin was a factor in producing the state of shock, she was subsequently tested with intravenous pitocin. As a result of this test there was no appreciable change in blood pressure, and no signs or symptoms of any systemic disturbance. It was concluded that the shock was the result of blood loss, which was relatively large for a debilitated and toxic patient, whose hemoglobin prior to delivery was relatively low.

SUMMARY AND CONCLUSIONS

1. The intravenous and intramuscular administration of pitocin produces no undesirable systemic effects.

2. The use of pitocin is not contraindicated in the toxemias of pregnancy.

3. Intravenous pitocin at the beginning of the third stage of labor induces a prompt and uniform contraction of the uterus which hastens the separation and expulsion of the placenta without evidence of trauma to the uterus or laceration of the placenta and membranes.

4. There is no increase in the incidence of retained placenta following the use of pitocin in the third stage.

5. The average total blood loss in 505 patients who received intravenous pitocin at the onset of the third stage was 171 c.c. and the average measured blood loss was 66.5 c.c.

6. The average total blood loss in 125 patients who received intramuscular pitocin at the onset of the third stage was 203.9 c.c. and the average measured blood loss was 83.3 c.c.

7. With the intravenous use of pitocin the average duration of the third stage was 5.4 minutes and with the intramuscular administration 6.5 minutes.

8. The intravenous use of pitocin in the third stage is preferred to the intramuscular injection because the oxytocic reaction occurs with greater rapidity.

9. The duration of the oxytocic action of pitocin is shorter than that of ergotrate.

I wish to thank Dr. J. P. Pratt for the opportunity of carrying out this study and for his helpful suggestions in the preparation of this paper.

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VAGINECTOMY*

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ONE of the major problems in operative gynecology is the selection of the operation best suited for the repair of hernias through the birth canal. The most important considerations are: first, the extent of the hernia; second, the age of the patient; third, the social state of the patient; and fourth, the patient's wish in the matter.

In cases of postoperative vaginal hernia and in cases of procidentia in which the patients are elderly women, especially if the procidentia is associated with a large cystocele or an enterocele,[8] it is often a difficult problem to replace the prolapsed organs and reconstruct a satisfactory vaginal canal. In many cases, if the patients will give their consent, the most satisfactory operation is one that will more or less close the vagina. Operations of this type are listed under the titles of "colpocleisis," "vaginectomy" and "colpectomy."

Vaginectomy necessarily results in a complete cessation of sexual relations and this should be explained to the patient and her husband. Most of the patients who were subjected to vaginectomy at The Mayo Clinic were past the menopause (the average age is 58.5 years) and had had multiple operations. The exposure and irritation of the vaginal mucous membrane had caused an unnatural dryness and thickening which usually had caused the cessation of sexual relations before the patients sought medical advice. The operation gives uniformly good results; it eliminates the bearing-down feeling, the discomfort, the urinary frequency, and the difficulty in emptying the

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rectum, which are cardinal symptoms of gynecologic hernia. The prospect of cure is all the patients desire.

Partial and complete vaginectomy has been done in Europe since 1877, when Le Fort described his operation under the title of partial vaginectomy. The first mention of the procedure in the American literature was by Edebohls, who called his operation panhysterokolpectomy. In the first case in which he performed the operation the patient had had many operations without relief. He reported 4 cases in which the uterus was removed along with the vagina; the results were uniformly good. Gallant reported a case in which the operation was performed. Demarest reported 10 cases in which the operation produced satisfactory results and described a technic of operation. Dujarier and Larget reported 15 cases in which the results of the operation were excellent. Simon reported a total of 92 cases, 2 of his own, in which a follow-up of 59 patients revealed that symptoms recurred in only one case. Baer and Reis in 1928 reported favorably on the results of the Le Fort operation in 14 cases. Rubovits and Litt in 1935 reported favorable results in 19 patients in whom a Le Fort operation was performed and in 1 patient in whom a total vaginectomy was performed. In 1935, Phaneuf wrote a paper on colpectomy in the treatment of uterine and vaginal prolapse.

It is surprising that so little has been written in this country on this important surgical procedure, as we are satisfied that it is used in at least a modified degree much more frequently than a perusal of the literature would lead us to believe. We are satisfied that in the majority of cases in which it is not possible to reconstruct a vaginal canal of approximately normal length, the surgeon is justified in closing the vagina if the patient will give her consent, especially if the patient is an elderly woman.

In a case in which closure of the vagina seems advisable and the uterus has not been removed at a previous operation, the surgeon has a choice of two operations: a complete colpectomy and a partial colpectomy. If a complete vaginectomy is contemplated and is considered the better operation, it is absolutely necessary to remove the uterus at the same time that the vagina is occluded. Even after the menopause, there is a certain amount of drainage from the endometrium and endocervix, which must be provided for if the uterus is not removed. Fortunately, a vaginal hysterectomy is very easy in this type of case as there is always marked prolapse.

In case a partial vaginectomy is advised, it will not be necessary to remove the uterus, but provision for uterine drainage must be provided. This is well cared for by the Le Fort operation, which obliterates the central portion of the vagina almost to the cervix and leaves a narrow open space on each side. There probably is a useful field for this operation as even some elderly patients will object to the removal of the uterus.

Besides these two types of vaginectomy, surgeons all know that following many vaginal hysterectomies[7] which are performed for marked

degrees of prolapse associated with large cystocele and high rectocele the upper part of the vagina is occluded in order to give strength to the closure. In many cases this shortening is just as much an inconvenience to the patient as is a total closure of the vagina and it is less likely to cure a gynecologic hernia than is the latter procedure.

TECHNIC OF TOTAL VAGINECTOMY

The technic of the operation varies considerably in the individual case, depending on what structures are available to close the opening. If the uterus is present, it is essential to remove it. After approximating the broad ligaments in the median line and firmly fixing them well up under the pubic arch, they can be sutured posteriorly to the levator ani muscles which are thoroughly freed and sutured in the

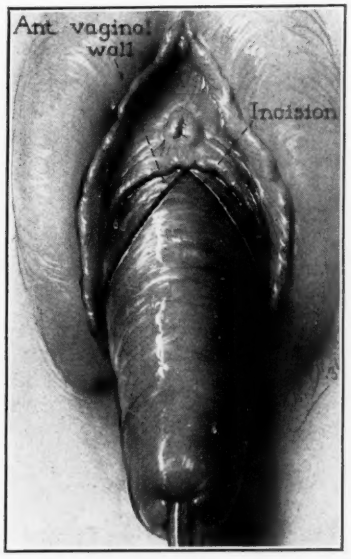

Fig. 1.

Fig. 2.

Fig. 1.—"V" shaped incision in anterior vaginal mucosa.
Fig. 2.—Circular incision of posterior vaginal mucosa at the level of the hymenal ring.

median line as they are in an ordinary perineorrhaphy. In this manner a strong pelvic floor is reconstructed and the closure of the rest of the vagina is easily accomplished, after removal of all mucous membrane, by interrupted transverse sutures, some of which are silkworm gut and are left in place for twelve to fourteen days. It is advisable to provide for drainage by inserting a small tube. If an enterocele is present, the peritoneal sac should be removed before commencing the closure.

If the uterus has been removed at a previous operation, it is often not necessary to open the peritoneal cavity. The mucosa is removed as advised previously. The levator ani muscles are approximated as in a perineorrhaphy and the pubovesical fascia and urogenital septum

are approximated in the median line and utilized to close the anterior part of the hernial opening and support the bladder. The denuded vaginal walls below this newly constructed pelvic diaphragm are approximated by interrupted transverse sutures, thus making a firm closure of what was formerly the vaginal canal (Figs. 1, 2, 3, 4, and 5).

The technic of the Le Fort partial vaginectomy is as follows: A strip of mucous membrane about 2 cm. wide is denuded from the anterior wall of the vagina from a point about 1 cm. below the

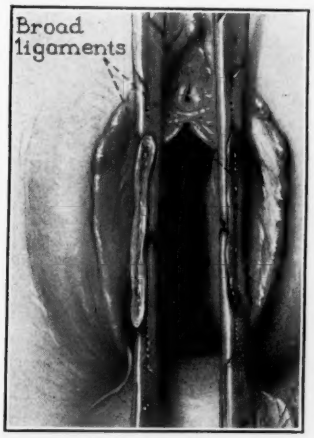

Fig. 3.—Approximation of broad ligaments when a vaginal hysterectomy is also done.

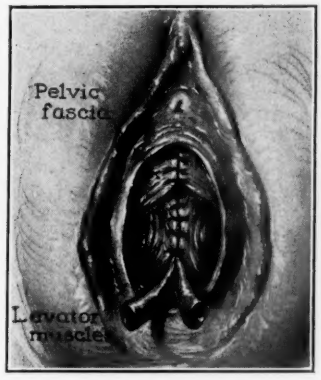

Fig. 4.

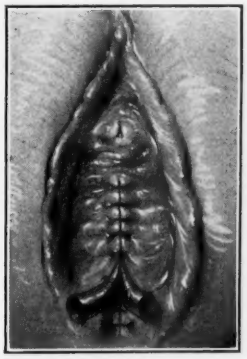

Fig. 5.

Fig. 4.—Approximation of levator muscles and pelvic fascia up to the pubic arch.
Fig. 5.—Approximation of mucosa; complete absence of vaginal canal.

urethral orifice to within 2 cm. of the cervical os. A similar area is denuded on the posterior vaginal wall. These two raw surfaces are accurately sutured together by commencing at the cervix and working upward and invaginating the prolapsed vagina, thus forcing the uterus upward. When the operation is completed there will be a mucous-lined tract from the cervix down each side of what formerly was the vagina. In all cases a high perineorrhaphy should be a final step in the operation (Fig. 6).

In the series of 23 cases in which complete vaginectomy was performed at The Mayo Clinic from 1910 to 1937, the oldest patient was 69 years of age and the youngest was 44 years of age; the average age of the patients was 58.5 years. In 7 patients a hysterectomy and vaginectomy were performed at the same time, while in 16 patients a vaginectomy only was done, as the uterus had been removed previously. Nineteen patients (82.6 per cent) were traced and found to be cured; 3 had some irritability of the bladder. No patient had a recurrence of the prolapse or hernia. Previous to operation this

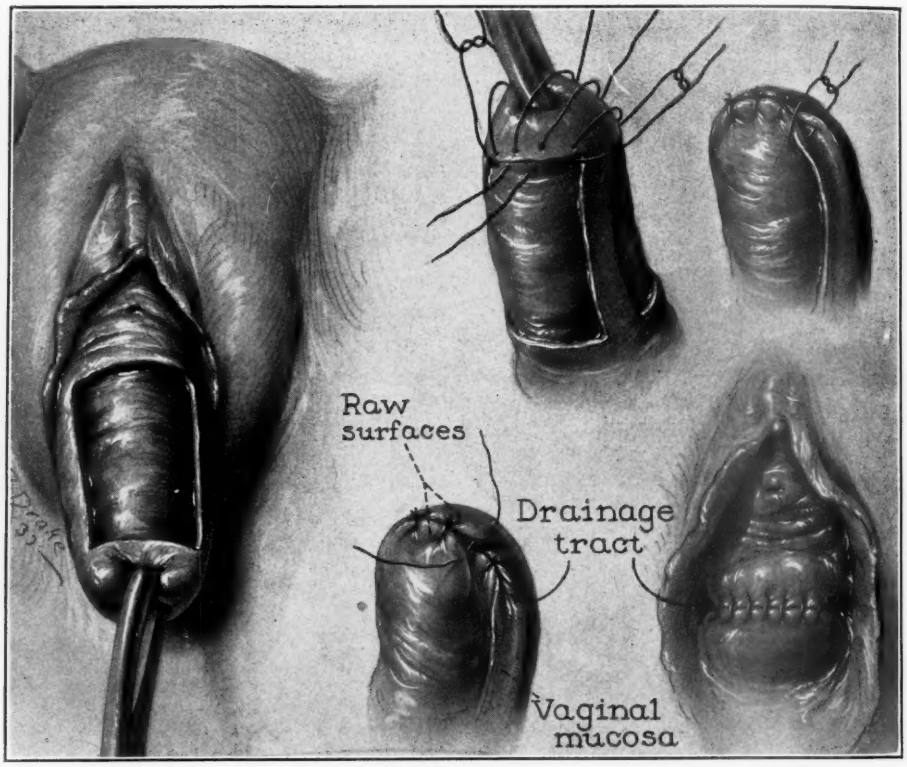

Fig. 6.—Technic of Le Fort's operation, showing partial vaginectomy.

group of patients had had 94 children, an average of more than 4 children per patient. One patient was unmarried and had not had any children; she had virginal prolapse. Seventeen patients had had previous operations for this condition, and 2 of them had been operated on four times. One patient died of pulmonary embolism on the thirtieth postoperative day. It just happened in this series there were no cases in which the Le Fort partial vaginectomy was performed. There is no doubt that it is a satisfactory operation in most cases but we believe the complete operation to be preferable. The removal of the uterus at the same time as the closure of the vagina adds very little to the operation.

CONCLUSIONS

1. In gynecologic hernias, the selection of the operation best suited to the individual case is important.

2. In the more difficult hernias which affect elderly patients some type of vaginectomy is justifiable.

3. Comparatively few cases of either partial or complete vaginectomy are recorded in American literature.

4. There is no doubt in our minds that a partial vaginectomy with removal of more or less of the upper part of the vagina is a rather common practice associated with a vaginal hysterectomy but that it is not reported.

5. The Le Fort operation with preservation of the uterus is a safe and satisfactory operation.

6. Complete vaginectomy with removal of the uterus is the operation of choice in many cases in which elderly women have procidentia of high degree and also is often indicated in cases in which vaginal hernia follows a previous hysterectomy.

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THE BILIRUBIN LIVER FUNCTION TEST IN THE TOXEMIAS OF PREGNANCY

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TWENTY cases of abnormal pregnancy in which hepatic function tests have been made at some period during the disorder is the content of this report. In an attempt to gain liver function information relative to the toxemias, the cases are essentially restricted to eclampsia, preeclamptic toxemia, nephritic toxemia, vomiting of pregnancy, and premature separation of the placenta.

Functional demands of gestation not infrequently embarrass not only the kidney but also the liver during the last trimester.[5] The ill-defined delimiting zone between normal and abnormal suggests the importance of individual tests in estimating the degree of latent or definite hepatopathy associated with abnormalities of the gravid state.

Observers[4, 5] who have had experience with several tests for hepatic function agree that the bilirubin retention method is the most sensitive

single test adaptable to clinical use. Utilization of a physiologic substance in a function similar to that continually demanded of the organ seems reasonable. This material is neither removed by the Kupffer cells nor excreted by the kidney.

That there is a notable limitation by the estimation of but a single function in an organ of manifold rôles is recognized.

Since von Bergmann[3] and also Eilbott[2] employed the excretion of intravenously injected bilirubin to ascertain the relative degree of hepatic function, there has been a satisfactory procedure for this purpose. Modifications by Harrop[4] and subsequently by Soffer[5] have been adopted. These investigators consider retention in excess of 5 per cent after four hours to be abnormal.

Soffer[5] and subsequently Sullivan[6] have shown evidence of a tendency to decreased excretion rate for bilirubin during the last half of gestation as compared with the initial half. The former observed an average of 1.6 per cent for the first half and 7.1 per cent during the second half of pregnancy. The latter attempted to differentiate the toxemias into predominantly nephritic and hepatic groups. An average retention of 19 per cent ante partum and 5 per cent post partum was reported.

METHOD

A resting blood specimen is drawn from an antecubital vein and immediately 1 mg. of bilirubin (Eastman Kodak Co.) per kilogram of body weight dissolved in 15 centiliters of 0.1 molar sodium carbonate is injected through the original needle. Five minutes later a specimen is drawn from the contralateral arm. A high bilirubin content will be observed in this second specimen; whereas the initial specimen contains lipochromes and possibly carotin. Upon subtracting the initial from the second value the introduced quantity or 100 per cent is obtained. After four hours a third sample is drawn which, after subtracting the initial value, is compared with the second and the result expressed in percentage of the quantity introduced. Using the colorimetric method of Ernst and Forster,[1] the bilirubin concentration is determined on the centrifugalized acetone precipitated plasma.

RESULTS

Showing an average bilirubin retention of 11.8 per cent four hours after injection this series of heterogeneous toxemias presents notably decreased pigment elimination as compared with the average of the normal pregnant series reported by Soffer.[5] Four of the group presented had eliminated all bilirubin administered within the test period. These included one individual classified as an example of essential hypertension, two patients with nephritis or nephritic toxemias and one instance of preeclamptic toxemia. Each of these four had some albuminuria and evidence of hypertension.

Noteworthy is the intrapartum test on a patient with premature separation of the placenta in which half of the dye was retained for four hours. This individual gave clinical evidence of marked toxemia and subsequently was delivered of a stillborn fetus after introduction of a Voorhees' bag.

TABLE I. BILIRUBIN RETENTION FOLLOWING INTRAVENOUS ADMINISTRATION

PATIENT	AGE	PARITY	WEIGHT KG.	E. D. C.	DELIVERY DATE	BILIRUBIN TEST DATE	BILIRUBIN RETENTION PER CENT	BLOOD PRESSURE	ICTERIC INDEX	FIBRINOGEN	URINARY ALBUMIN	REMARKS
Eclampsia												
H. L.	33	1	79.4	7/ 1/36	5/25/36	5/23/36	8.4%	190/120	10	0.60	4+	Prem. 1 mo. Labor induced 4 da. after convulsions.
H. B.	34	13	96.8	6/10/36	4/26/36	4/24/36	9.5%	210/100	8	0.46	4+	Prem. 2 mo. Convulsions on admission.
*M. D.	17	0	53.6	8/28/35	7/29/35	8/ 5/35	11.4%	150/110	3	0.39	1+	Post partum (18 hr.) recurrent eclampsia.
C. N.	31	0	58.7	4/29/36	4/ 7/36	4/ 8/36	7.6%	160/ 90	10	0.20	4+	Intrapartum eclampsia.
Vomiting of Pregnancy												
H. M.	25	1	64.8	11/ 6/36	5/ 6/36	5/ 5/36	37.4%	138/100	24	0.47	0	Ther. abort. Died 5/11/36. Icteric index 8 on 5/11/36.
M. S.	30	5	84.6	11/19/36	11/29/36	5/ 8/36	9.2%	120/ 78	12	---	trace	Tox. vomiting, acetone +, diacetic 4.
R. T.	22	0	59.2	6/27/35	6/21/35	11/ 9/34	25.9%	120/ 80	10	0.55	trace	Acet. 4, Diacet. 4.
Pre-eclamptic Toxemia												
I. M.	35	1	75.4	8/20/35	8/21/35	8/18/35	4.0%	140/100	6	---	3+	Induction of labor 8/21/35.
E. P.	19	0	71.0	1/23/35	1/11/35	1/11/35	0	132/ 90	8	---	trace	----------
J. G.	34	7	71.5	3/27/36	--------	3/10/36	7.0%	210/100	8	0.27	4+	Died in labor, 4/11/36; ? pre. sep. pla.
J. G.	19	0	77.0	3/18/36	2/11/36	1/30/36	14.9%	145/ 84	--	---	2+	----------
Premature Separation of Placenta												
S. K.	25	0	45.8	9/17/35	8/21/35	8/20/35	51.0%	140/100	12	---	4+	Vorhees' bag induction of labor.
Pregnancy Abnormal With Nephritis												
A. K.	27	1	90.0	8/17/35	8/15/35	7/23/35	0	190/130	--	0.45	2+	----------
K. P.	32	0	68.0	8/ 3/35	8/ 8/35	7/11/35	10.9%	182/100	--	---	1+	Urine cult. anaerobic strep. mac. fetus. Macerated fetus
M. E.	42	7	59.4	5/17/36	4/11/36	3/ 6/36	0	240/128	6	0.52	4+	Premature delivery.
M. G.	34	1	44.6	3/10/36	3/11/36	3/ 3/36	12.1%	122/ 84	6	---	0	Cesarean section for sterilization.
F. M.	39	3	100.0	1/21/36	1/18/36	1/15/36	3.2%	160/ 90	--	0.31	trace	Hypochr. anemia, sec. hyperten.
N. M.	31	2	58.3	6/19/35	11/ 9/34	9/12/34	15.4%	132/ 82	--	0.23	1+	Supravag. hysterectomy of gravid uterus.
Missed Abortion												
I. W.	28		57.0	10/20/35	7/ 4/36	6/29/36	7.9%	130/ 80	6	0.10	0	Spon. abortion following transfusion reaction.
Essential Hypertension												
L. G.	34	3	74.0	4/27/35	3/23/35	3/18/35	0	165/110	6	0.44	trace	Induction of labor, prem. delivery.

*Fibrinogen 0.63 on 8/2/35.

The vomiting of pregnancy group averaged a 24 per cent retention of the dye in the allotted time. These tests were carried out during the first trimester of gestation. Increases in the icteric indices were noted in all of these cases. Where tests for acetone bodies were done, positive findings were present.

Pre-eclamptic toxemia in this series shows an average retention of 6.5 per cent during the latter weeks of pregnancy. Albuminuria and a tendency of hypertension were observed in the last few weeks of pregnancy in each instance. The previous history had been negative for disturbances during late pregnancy and the abnormal findings were restored to normal limits upon discharge. Transient edema of the hands and face was occasionally recorded but no edema of the fundus occuli was noted. Renal function as determined by urea clearance and Addis cast counts were not remarkably abnormal in this group.

Eclampsia as reflected in bilirubin elimination tests carried out at various times near or following the date of delivery gives an average retention of 9.2 per cent which is about twice the normal limit. Although normal pregnancy may present an increased bilirubin elimination time,[5] in this group there were no normal cases. A definite but slight tendency to diminished liver function is indicated in eclampsia. Blood pressure was consistently elevated, often to a marked degree. Furthermore notable albuminuria was present in every instance. The tendency to increased icteric index values was not marked. Fibrinogen determinations show an average of 0.41 mg. per cent and a correlation with the dye test is not established.

Chronic nephritic toxemia as manifested in bilirubin function presents an average retention of 6.9 per cent which is somewhat more than that established for normal pregnancy, but individual variations ranged from 0 to 15.4 per cent. Well recognized are the difficulties in diagnosis in this group. Frequently proper classification is definitely established only after careful studies many months post partum. Although the relatively early onset, history of previous episodes during an antecedent pregnancy, and chronic course suggested a nephritic basis, in some instances at least there was a significant retention of injected bilirubin. Where examinations of the fundi were recorded, the only abnormalities were vascular. The urea clearance and Addis cast count procedures gave values which were usually diminished. The albuminuria was variable quantitatively. No edema of significance was reported. Hypertension was usually marked, although two instances of consistently moderate pressure readings are noted.

As presented in the table, an instance of missed abortion was tested six days prior to expulsion of the fetus. Slight retention (7.9 per cent) was observed with no increase in icteric index or primary evidence of toxemia.

Remarkable is the striking retention amounting to 51 per cent found in an individual with outspoken clinical signs of premature separation of the placenta. There was hypertension and marked albuminuria together with an elevated icteric index of twice the upper normal

limit. With the sudden onset, this instance of acute toxemia displayed within a few hours pronounced symptoms of a critical disturbance only to subside rapidly subsequent to termination of the induced labor.

A single instance of decided hypertension presented no hepatic dysfunction, nor were the associated tests abnormal.

DISCUSSION

The icteric index may be elevated in liver dysfunction but in disturbances of some days' duration the tendency is toward subsidence even though the bilirubin elimination remains delayed. Apparently it varies from case to case but properly interpreted may be a gross guide to the bilirubin excretion capacity of the liver. In the presence of persistent clinical icterus there is ordinarily no indication for a bilirubin excretion test.

Fibrinogen values are frequently low in experimental hepatic damage in dogs, but no correlation was established with bilirubin excretion values in this series.

Nephritis during pregnancy would not be expected to show altered bilirubin excretion, especially since the dye is not eliminated by the kidney in man. However, it is possible that the pregnancy liver of earlier writers is disturbed to a variable extent during the altered metabolism of the final trimester in instances of chronic nephritis. It seems unnecessary to postulate the coexistence of two entities.

As an alternate possibility the several instances of increased retention may eventually show normal kidney findings and future normal pregnancies. This would suggest a reclassification as pre-eclamptic toxemias.

SUMMARY

Toxemias of pregnancy cannot be nosologically arranged on the basis of the bilirubin hepatic function test. However, this procedure is probably our most adaptable measure of the labile and manifold functioning liver. As such it may be of value together with renal function tests to aid in establishing a delimiting zone between the nephritic and pre-eclamptic toxemias.

CONCLUSIONS

Hepatic function tests by the bilirubin elimination method have been studied in twenty cases of abnormal pregnancy in which the average retention was 11.8 per cent.

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THE POTENTIAL BISEXUAL CHARACTER OF THE OVARY*

A Preliminary Report

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IN PREPARATION for the development of the genital system each embryo, whether it be "determined" as male or female, provides itself with materials from which may develop the organs of either sex, that is, paired gonads, two mesonephroi (Wolffian bodies) with their ducts, and the paired Müllerian ducts. To produce male generative organs the gonads become progressively developed into testes, the mesonephric tubules become the efferent ductules of the epididymides, and the mesonephric ducts transform into the vasa deferentia. The Müllerian ducts degenerate wholly or, in part, remain as vestigial structures. Reciprocally, in the event of female development, the gonads become markedly modified to produce ovaries, the Müllerian ducts remain, while the entire mesonephric apparatus partially degenerates and persists vestigially.

For a better understanding of the subsequent observations a brief detailed description of the development and differentiation of the gonad into the ovary or testis is necessary. As a result of cellular proliferation of the mesothelium covering the ventromedial borders of the urogenital folds in the embryo, paired longitudinal prominences, the genital folds, are produced. Continued development and expansion of the genital folds produce oblong gonads suspended from the ventromedial sides of the mesonephroi. Each gonad is composed of: (1) a mesothelial covering (germinal epithelium) which has formed (2) an inner epithelial mass and (3) rete cords. In the differentiation of a testis the inner mass becomes separated from the germinal epithelium by the formation of an intervening connective tissue tunica albuginea. The inner mass becomes cordlike due to the appearance of septa and later becomes the testis tubules. The rete mass or cords transform into the rete testis, connecting distally with the testis cords and proximally with the cranial group of mesonephric tubules. Germinal cells and Sertoli ("nurse") cells develop in and from the epithelial testis cords. Male interstitial cells originate from the surrounding connective tissue cells (Wilson) or from the germ cells which are not included in the tubules (Simkins). It is probable that in either case the production of interstitial cells is dependent upon influences exerted by the medullary cords (testis tubules).

If an ovary is to be differentiated, the tunica albuginea does not form and therefore the germinal epithelium is permitted to continue its proliferation of cells upon the central epithelial mass, thus producing an outer cortex (zona parenchymatosa). The rete ovarii develops from the rete mass and does not, according to Felix, connect with the mesonephric tubules. The lateral portion of the ovary, containing the rete, is homologous with the superior pole of the testis. Degeneration of the central primary epithelial mass in the interior of the gonad supposedly early removes all of the gonadal or testicular material surrounding which the future ovarian cortex is formed. According to most textbooks the

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rete ovarii degenerates as well; Wilkerson, however, has shown the rete ovarii to be a normal constituent of the adult mammalian ovary.

Without becoming involved in a consideration of the complex problems of the determination, differentiation, and maintenance of sex and secondary sex characters, certain fundamental facts may be expressed: It is apparent that the gonads of all embryos are identical. In becoming testes the gonads suffer no radical alteration in original structure plan. On the other hand, ovary formation necessitates a later and secondarily superimposed addition of cortical tissue from the surface germinal epithelium upon the centrally displaced primary gonad. Further, male characteristics appear earlier than those of the female, a beautiful functional example of which is exhibited in the free martin. It follows, then, that the gonad is primarily male and that the female condition is a secondary one. Recent biologic concept tends to strongly favor this interpretation. If a hermaphroditic or bisexual condition is existent, it must be ascribed to the female since there the sex gland possesses the primary gonad (male) as well as the secondarily added ovarian material.

Under certain normal developmental influences one sex predominates, such predominance being manifested by the definitive structure of the genital organs and secondary sexual characters. It is probable that completeness in reciprocal degeneration and growth is rarely produced and that varying degrees of low grade intersexuality occur normally, as evidenced by rests of primary gonadal material in the ovary and vestiges of the two paired ducts in both sexes. Evidence from the ovotestis in certain intersexual conditions likewise indicates that total degeneration of the primary gonadal tissue did not take place, since material capable of producing testicular tissue must have been left. Therefore, the extent of the degeneration or retention of this material in development is most significant. Such embryonic tissue would be expected, within normal limits of variation, to be found in the lateral half of the hilus of the ovary—in a position corresponding to the mediastinum (and its contents) of the testis with which its homology is apparent. The possibility is present, then, of the persistence of gonadal remains in all ovaries, and particularly in cases exhibiting degrees of male characteristics. This investigation was undertaken in an attempt to determine if such is actually the case.

Ovaries taken at autopsy from normal women (14 to 44 years of age) were sectioned serially and studied.* The rete ovarii was found to be present in all cases. It is located usually in the lateral half of the hilus of the ovary (Fig. 1), although many times it extends into the adjacent mesovarium to attach to the tubules of the epoophoron (70 per cent). Intimately related to the rete ovarii groups of epithelioid cells strikingly similar to interstitial cells of the testis and epididymis are regularly encountered. When present in moderate amount, they are always in the

*Grateful acknowledgement is made to Dr. Martin J. Crane for his generous cooperation in this study.

vicinity of the rete (Fig. 1), but when occurring in increased numbers, they may be scattered throughout the ovarian hilus and the related mesovarium as well (Fig. 2).

These cells have been mentioned by other investigators. Wallart has illustrated cells, labelled "paraganglionic," near the rete ovarii and usually at the lateral pole of the ovary. Berger has termed them "sympathicotropic cells" and believes them to be related to the sympathetic nervous system. Kohn has pointed out their similarity to male interstitial cells and feels that they should be compared to the extra-

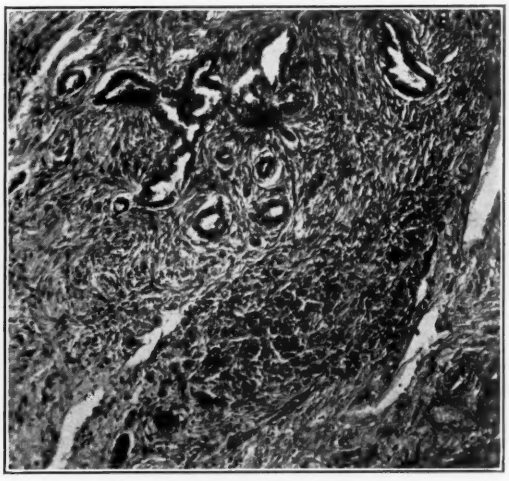

Fig. 1.—Photograph of a mass of male interstitial cells adjacent to the rete ovarii in an ovary from a 44-year-old woman. Magnification 100×.

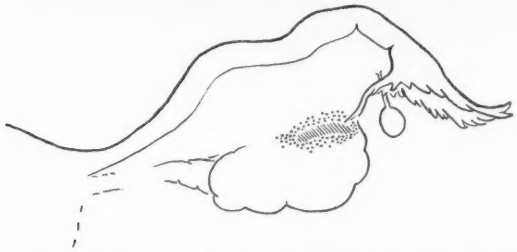

Fig. 2.—Drawing of the ovary to illustrate the position of the rete ovarii and interstitial cells. The closely lined area represents the usual position of the rete. The distribution of interstitial cells is shown by stippling.

glandular interstitial cells of the testis. Also, Kohn believes these cells to originate from the germinal epithelium. The contention that we are dealing with sympathetic or chromaffin tissue is seriously questioned after cytologic study. Female interstitial cells originate from the connective tissue theca during the atresia of ovarian follicles (Kingsbury) and rarely come to lie in the hilus or the mesovarium. Further, since female interstitial cells are extremely infrequent in the human ovary and are easily recognizable when present, it is impossible that they are being dealt with here. Adrenal cortical tissue was not encountered in these ovaries.

Attached to the rete ovarii in the lateral portion of the hilus of an ovary from a 34-year-old woman exhibiting signs of virilism, there were found a number of epithelial cords which strongly suggest medullary cords of the gonad and the testis cords of the primitive testis (Fig. 4). In this structure no cells which could be identified with certainty as germinal or Sertoli cells were seen.

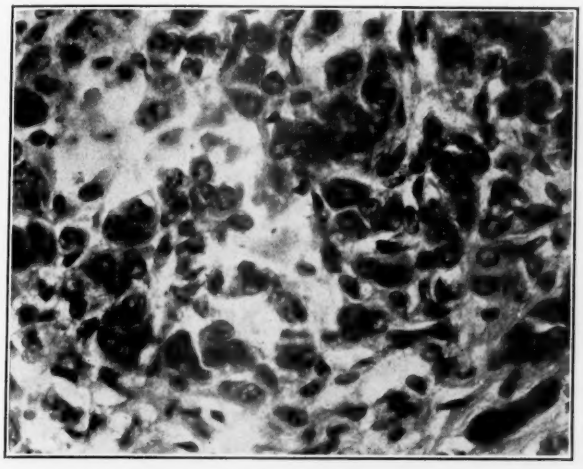

Fig. 3.—Photograph of male interstitial cells from the region of the rete ovarii in an ovary from a 22-year-old woman. Magnification 500×.

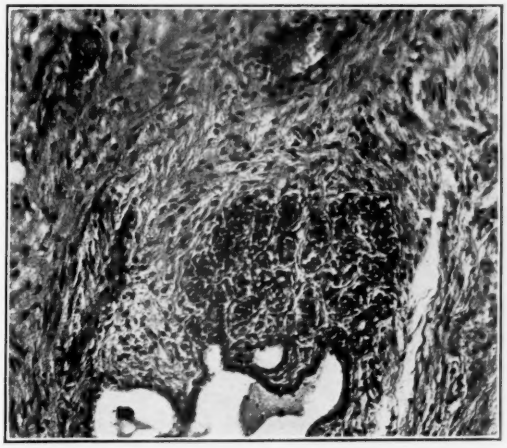

Fig. 4.—Photograph of epithelial cords attached to the rete ovarii from a 34-year-old woman. This structure was found in the lateral pole of the ovarian hilus. Magnification 100×.

There is a correlation between the amount of retained vestigial mesonephric material (actually male duct material) in the ovaries of normal women and the amount of rete ovarii and associated cellular formations. Ovaries related to large masses of epoophoron, paroophoron, cystic remains of Gartner's duct, etc., usually possess large accumulations of primary gonadal remains as well. Such findings are in keep-

ing with those prevailing in certain intersex conditions and are interpreted as being due to the activity, probably hormonal, of retained primary gonadal (essentially testicular) tissue which affects retention, growth, and differentiation of the male duct representatives as well as producing possible changes in the genitalia and secondary sex characters.

CONCLUSIONS

The ovary, particularly early in development, is interpreted as essentially bisexual, and in this is subject to wide individual variation.

Both the cellular elements described previously, interstitial cells and rudimentary testis tubules, are considered here to represent undegenerated gonadal materials which have become definitely testicular in direction of differentiation. In the light of the evidence obtained from this study the primary condition of the gonad is believed to be male. Other factors pertinent to the problem of sex must, for obvious reasons, be omitted here.

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ELEVENTH AND CLINTON STREETS
1534 PINE STREET

VIRILISM AND FEMALE PSEUDOHERMAPHRODITISM WITH RELATION TO THE BISEXUAL NATURE OF THE OVARY*

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THE manifestations of virilism range from slight facial hypertrichosis in otherwise normal women to such malelike characteristics as abundant growth of hair on the face, chest, abdomen and extremities, hypertrophy of the larynx, deepening of the voice, regression of the breasts, and enlargement of the clitoris. The menstrual function may be markedly disturbed or totally suppressed.

Pronounced types of virilism may occur as the result of tumors of the basophilic cells of the anterior pituitary, the cortex of the adrenal or the medulla of the ovary. Such lesions should be suspected particularly when symptoms of virilism arise in children or adult women or if an existing virilism becomes accentuated.

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In what may be called the ordinary form of virilism, the abnormal secondary sex characteristics appear at about the age of puberty, reach their maximum during adolescence, and then remain stationary.

Female pseudohermaphroditism is a condition in which the external genitalia resemble the male type, although the ovaries and other internal genital organs appear to be structurally normal. Virilism usually occurs during adolescence in female pseudohermaphrodites and creates additional difficulty in the recognition of the true sex.

Ordinarily the common form of virilism and female pseudohermaphroditism are not considered to be related conditions but the one may be regarded as an adult form of masculinization and the other a fetal type of the same phenomenon. In this light these two abnormalities will be discussed with relation to the bisexual nature of the ovary.

Pertinent to this discussion are certain factors concerning arrhenoblastomas, often called masculinizing tumors, which originate from the medulla of the ovary. Meyer describes two types of these neoplasms, one in which epithelial lined tubules are prominent and another composed of rudimentary cords of cells; and says that the latter type is invariably accompanied by marked physical signs of masculinization while with the former such effects may be slight or absent. McLester expresses this seemingly paradoxical relation by stating that those tumors with the least microscopic resemblance to testis show the greatest masculinizing effects.

A somewhat similar situation, although not so sharply defined, exists in the two forms of intersexuality of fetal origin encountered in women; both present the common feature of varying degrees of malelike formation of the external genitalia. But in true hermaphroditism, in which an ovotestis is present, there may be a little evidence of somatic intersexuality, i.e., the body form and breasts may be feminine in configuration; while in female pseudohermaphroditism, a condition in which the ovaries are apparently normal, the body form, especially the upper portion, and the breasts, may closely resemble the male type. Furthermore, at adolescence in the first instance beard growth may be slight or may not occur while in the second it is likely to be pronounced. An example of each of these types will be described in a later section of this paper.

In view of this peculiar distinction in the abnormal sex hormone effects which characterize the two types of these abnormalities, a consideration of certain etiologic factors is of interest.

Meyer believes that arrhenoblastomas originate from undifferentiated germ cells which are not utilized during embryonic development but which retain their sexual potency and under certain external conditions of unknown nature start to proliferate, and then only begin to exert an influence in the direction toward maleness.

This view is based upon the thought that the primary gonad, which is common to both sexes, is composed of physiologically indifferent cells, which, however, are inherently capable of development into either of the two distinctive sex glands. If this is true it then follows that a

condition of potential hermaphroditism exists during this early stage of gonadal development in every embryo.

This conception is no longer biologically acceptable. Certain animal experimental findings indicate rather that the primary gonad, in both sexes, is testicular in nature. In males it develops into a testicle. In females the cortex of the ovary arises from other cells which grow around the primary gonad which is eventually reduced, theoretically, to a vestigial state.

With regard to this subject Willier, for example, states that it is clear from the structure of the ovary of birds and mammals that it has a bisexual organization. The first set of sex cords which constitute the medulla is morphologically equivalent to the sex cords of a testis, whereas the cortex is distinctly peculiar to the ovary. Moreover, the medulla is potentially a testis as it has been possible to stimulate the first sex cords to form seminiferous tubules. True hermaphroditism, therefore, occurs only in those animals that were destined to be female and is essentially a condition of abnormal development of the primary gonad.

This conception is the more applicable to the conditions of sex reversal encountered in human beings with regard both to diagnosis and therapy. The weight of clinical evidence supports the view that in man, as in the higher animals, true hermaphroditism occurs only in those who are female in the genetic sense.

Another indication that the human ovary is bisexual in nature is the fact that testis hormone seems to be a constant constituent of the urine of women. The crude urinary extracts of testis hormone, which when injected into capons cause increase in the size of the comb, are now called androgens. Various workers have found androgen in the urine of normal women in amounts approximately equal to those found in the urine of men.

In cases of virilism this substance is present in the urine in amounts appreciably greater than found in the urine of men according to the studies of Bühler; Simpson, de Fremery and Macbeth; and McCahey, Hansen, and Soloway.

The last named also studied the androgen content of the urine in two cases of hermaphroditism, in both of which the external genitalia simulated the male type. In one case the body form was masculine, the breasts were flat, and hair growth was present on the face to a degree which necessitated frequent shaving. Assays of the urine for androgen showed it to be present in amounts greatly in excess of those found in men. Operation by Dr. Catherine Macfarlane, at the Women's Medical College Hospital, showed the uterus to be small but the tubes and ovaries appeared to be normal. Section of the cortex of one of the ovaries was reported normal ovarian tissue.

In the other case the general body configuration was feminine, the breasts were developed, and there was only scant growth of hair on some parts of the cheeks. Androgen was present in the urine in amounts approximately equal to those found in normal men. Operation by Dr. E. L. Eliason, at the Philadelphia General Hospital, disclosed an

undeveloped uterus and an abnormal appearing gonad on one side which on microscopic examination was identified as an ovotestis.

These two cases are illustrations of the observation that female pseudohermophroditism may exhibit more marked stigmas of somatic masculinization of both fetal and adult origin than true or glandular hermaphroditism.

From what has been said with regard to the equality of testis hormone elimination in the urine of both normal women and normal men, it might appear that rudimentary remnants of primordial testis tissue in the ovary possess an endocrine function as potent as that of normal testes. However, the degree of utilization must be considered. The androgen found in the urine of normal women may represent the entire amount elaborated while that found in the urine of men may represent only the portion of the total secreted which was not utilized in the maintenance of the male gonads and the accessory sex apparatus.

The factor of utilization is probably also of significance in connection with the relatively slight masculinizing effects in the two affections of women associated with the presence of testis-like tissue, namely, the tubular form of arrhenoblastomas and glandular hermaphroditism. It is reasonable to suppose that the major portion of the elaborated hormone is utilized in the maintenance of these seminiferous tubular structures.

With regard to the occurrence of more marked signs of masculinization with both the cellular form of arrhenoblastomas and female pseudohermaphroditism certain questions arise: Are the abnormal sex accompaniments of both due to endocrine activity of embryologically analogous cells of primary gonadal origin? Are such cellular structures present in the ovaries in cases of female pseudohermaphroditism and the common form of virilism?

That such tissue is present in the ovary in both these conditions appears to be a reasonable supposition solely on the basis of the clinical features which have been discussed. Testis hormone investigations lend further support to this view, although the evidence with respect to these is incomplete because of the paucity of such studies from the standpoint of clinical investigation.

The possibility of the presence of testis-like tissue in the ovary is frequently mentioned in articles dealing with conditions of sex reversal in man, but such references have been with regard to the rete ovarii, which is analogous with the rete testis, a structure which has to do with neither spermatogenesis nor hormone secretion. The rete ovarii is a well-recognized embryologic structure but the usual teaching is that it disappears at birth although occasionally it persists until puberty.

In the investigations of this problem carried out by Ramsay and McCahey, the rete ovarii was found in all the ovaries of normal adult women which were examined and in association with it there were cells apparently similar to the interstitial cells of the testis. In an ovary from a case of virilism, a structure composed of cells in an arrangement strongly suggestive of rudimentary testicular tubules or gonadal medullary cords was found connected with the lateral portion of the rete.

In the majority of specimens studied, these structures were situated in the hilus of the ovary in the lateral half and sometimes extending into the adjacent mesovarium.

As the location of this tissue was usually found to be such that extirpation appears to be feasible, the suggestion seems warranted that further study may show that beneficial results may be obtained in cases of both female pseudohermaphroditism and the common form of virilism by surgical removal of the lateral portion of the ovaries including the hilus and adjacent portions of the mesovarium.

With regard to those cases of virilism dependent upon tumors of the adrenal or the anterior pituitary, it is not clear whether the masculinizing effects are primary or secondary. Neither of these glands are known to secrete a sex hormone, but in the case of the anterior pituitary, a sex-stimulating function is well established. Bruins Slot has recently reported a case of tumor of the left adrenal associated with virilism. A large amount of androgen was found in the urine, but assays of the tumor after removal failed to show the presence of either sex hormone.

The suggestion is made that those who have the opportunity to study such cases at autopsy examine the ovaries with reference to the cellular structures around the rete ovarii.

CONCLUSIONS

1. It is suggested that, in cases of the common form of virilism and cases of female pseudohermaphroditism, study of the ovaries for the presence and location of primordial testis tissue be made with the view of determining the possible advantage of removing this tissue by surgical means.

2. The suggestion is made that when cases of virilism associated with tumors of the adrenal or anterior pituitary come to autopsy that examination of the indicated portions of the ovaries be made part of the routine investigation in order to ascertain the relation of these cells to the primary growths.

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DISCUSSION ON PAPERS BY RAMSAY AND McCAHEY, AND BY McCAHEY AND RAMSAY

DR. DAVID M. DAVIS.—There is so little about the gonads which can be proved from their histologic appearance. We hear, for example, about ovarian interstitial cells. These apparently arise from the cells of the theca and are therefore entirely different from the interstitial cells in the male. They are sometimes present in small numbers in the adult, but there is no way in which their function can be

studied. We understand the function of the interstitial cells in the male, because if the testicle is undescended, the tubules degenerate, but there is no comparable situation in the ovaries.

There is considerable dispute about the origin of the male interstitial cells. Do they arise from the connective tissue or from certain of the genital cells not included in the cell cords which go to make up the testicular tubules?

The genitaloid cells at certain periods seem to stand out distinctly in the mass of the testis. They are to be found in the embryonic male gonad and also after the age of puberty but, according to the best authorities, between birth and the age of puberty they are not to be found. What happens to them in this interlude? Do they disappear or disguise themselves and then reappear at puberty? If they degenerate in embryonic life, what then is the cause of their reappearance at puberty? These genital cells, about which we can say very little except that they have a characteristic appearance, are to be seen in the rete blastema up to 55 mm. in length in the male, and they then disappear and the rete goes on to form cords. If these cells in the main body of the testis can disappear at birth and reappear at puberty, why can they not do the same in the rete? Yet, if they are an entirely new development instead of a reappearance of disguised cells, their significance in the male would be just as obscure as in the female.

After all the rete ovarii is apparently a normal structure present in every ovary. It is vestigial, but so is the epoophoron. These structures are always to be found and their presence casts no doubt, of course, on the female nature of the individual bearing them. Since they have an origin which is analogous to the origin of the cells in the male, perhaps they are the homologue of the interstitial cells in the male. They belong there and the ordinarily spoken of ovarian interstitial cells are something else with a different function.

DR. SIDNEY DUNNE.—Considerable work by Koch and many other workers has been carried out in male hormone assays in men and women, both normal and those with certain pathologic conditions associated with virilism. Results in this work vary considerably. According to Koch, it is impossible at this time to support the theory that virilism is due to a hypersecretion of a recognized comb-growth stimulating hormone. While it has been proved that the gonads are the main source of male and female sex hormones, yet in castrated men and women such hormones can be detected in the urine. Moreover, in cases of virilism due to adrenal tumors, the tumor itself, as Dr. McCahey has shown, has failed in some instances to contain an excess amount of male hormone. Thus, until we know more about the chemistry of male and female sex hormones no definite conclusions can be shown with regard to the source or role of the androgenic hormone in virilism.

With regard to the arrhenoblastoma, or masculine-like tumor of the ovary, very few cases have been reported in this country. Baldwin and Gafford have collected all the cases in the literature up to 1935 and found 34, including their own. A few cases have been reported since their paper. No male hormone assays have been carried out in these cases to allow any discussion on this point. The interesting fact connected with this tumor, as Dr. McCahey has shown, is that the most differentiated type shows no, or very slight, masculinizing effect while the type which resembles testicular tissue most is always accompanied by marked virilism.

DR. CHARLES MAZER.—An excess of male sex hormone (testosterone) said to be present in the urine of patients suffering from arrhenoblastoma, does not prove that the excess of the hormone is directly responsible for the syndrome of virilism. Reproduction of the syndrome by the administration of testosterone would prove the point. I have found, however, that the administration of 2½ to 25 mg. of testosterone every other day for a period of months, for the purpose of arresting benign menopausal uterine bleeding, does not produce virilism. Its effect is apparently limited to the generative organs wherein it produces hypoplasia and arrest of the benign uterine bleeding.

I want to stress the inadequacy of our present method of determining the quantity of male sex hormone in the urine of patients showing a tendency to masculinity. The "comb unit" is so large that one can employ only two or three

capons in a given test. Animals are known to vary greatly in their response to hormone injections. Some are highly sensitive; others are not. It is, therefore, necessary to employ 12 to 15 animals in a given test to be accurate.

DR. CHARLES WILLIAM DUNN.—Dr. Ramsay's findings clearly indicate the actual and potential bisexual character of the ovary which is very important from an endocrinologic viewpoint. Grollman and others consider the rete ovarii as androgenic tissue. Therefore, this tissue biologically corresponds to the androgenic zone of the adrenal cortex, the adrenal cortical rests, and the accessory adrenal cortical masses. Besides an embryologic, histologic, biologic, and chemical correlation, we find that pathologic lesions of androgenic tissues present a marked clinical similarity. This is prominently exemplified by the Cushing syndrome.

My first illustration is that of a female, aged 62 years, with arrhenoblastoma of the ovary. The virilism, hirsutism, hypertension, and the regional type of obesity is that observed in the Cushing Syndrome, whether it be due to pathology of the anterior pituitary basophile cells and the associated adrenocortical pathology or to carcinoma of the adrenal cortex or the thymus gland. This patient also had a hypertrophied clitoris. This abnormality is more frequently found in virilism and the adrenogenital syndrome.

Broster of England has shown that in most cases of adrenogenital syndrome a marked hypoplasia of the uterus and ovaries is present and is clinically exhibited by amenorrhea or diminished menses and subjective signs of the hypoovarian state. A similar genital pathology and dystrophy exist in the Cushing syndrome, thus we may have in pituitary basophilism or Cushing syndrome, amenorrhea and an abnormal contour corresponding to that of pregnancy.

Pregnancy produces a physiologic hyperplasia of the anterior pituitary lobe, the adrenal cortex, and the thyroid internal secretory cells. If the endocrine hyperplasia regresses to normal after delivery no untoward signs develop; however, if the hyperplasia persists endocrine disorders of the above type may appear.

In a series of 11 patients whom I have diagnosed clinically as Cushing syndrome, there were 9 married and 2 single females. I obtained a history of the onset of this syndrome directly following pregnancy in 5 of the 9 married women. In cases of virilism and androgenital syndrome, I also found that pregnancy quite frequently preceded the onset of symptoms. The tendency to virilism at the menopause again illustrates the potential androgenic nature and the bisexual character of the female.

As to the etiology of virilism, Broster reports the isolation by Marrion and Butler (Toronto) of a new chemical which is an androgen and different in character from those previously isolated. This androgen has only been present in cases of the adrenogenital syndrome, and it disappears or diminishes following unilateral adrenalectomy. This substance has not been previously found in the urine of either sex or in pregnancy urine. The chemical formula of this substance is $C_{21}H_{26}O_2$.

Adrenal hypercortical disorders are not always associated with obesity as is evidenced by the leanness of this girl of 9 years of age with a hypertrophied clitoris. Another significant clinical feature in this case is the marked tendency to extensive spontaneous purpura. We also know of the precocious onset of menses in adrenal hypercortical disorders and the early history of excessive menstrual bleeding occurring in many of the cases. This factor of excessive bleeding or disturbed coagulation of the blood might explain the unusually severe metrorrhagia of the case of virilism reported this evening by Dr. Rheuby.

The next case is that of an adult female, aged 29 years. The emaciation was extreme and strikingly simulated that of Simmond's disease. However, the marked hypertrichosis, the hypertrophied clitoris, primary amenorrhea, and abnormal hyperplasia and dysplasia of the internal genitals, differentiate it from Simmond's disease.

Dr. McCahey suggests a very rational surgical procedure in proposing excision of the site of the rete ovarii in cases of virilism and adrenogenital syndrome. It is well known that many of these patients do not respond to unilateral adrenalectomy, therefore it is quite possible that as long as rete ovarii remain in the ovaries suf-

ficient stimulation of them may and can occur and the clinical syndrome persists. If this area of the ovaries described by Dr. Ramsay as the usual site of the rete ovarii is excised, we are definitely removing a probable cause and thereby lessening the chance of unsuccessful surgical therapy.

Adrenal cortical disorders occupy an important place in the differential diagnosis of obstetric and gynecologic conditions. Therefore I feel this evening's presentations are a definite advancement towards our clinical understanding of this very important group of pituitary-adrenal-gonadal disorders.

DR. RAMSAY (closing).—Among the many descriptions of the origin of male interstitial cells, origin by direct transformation of the interstitial connective tissue cells is a most interesting and probable one. During inflammatory processes in the testis, series of close transitions between connective tissue and male interstitial cells have been seen. Such possibilities, no doubt, explain the facility with which the interstital cells may fluctuate in number. The suggestion that these cells develop from the original gonadal genitaloid cells not included early in testis tubules, I think, should not be cast aside.

In all fairness to those holding opposite views, I would like to mention that the actual function of the interstitial cells has been questioned, particularly those of the female. It is well known that interstitial cells in the human ovary (admittedly homologues of male interstitial cells) are extremely rare and may be absent entirely. Such individuals exhibit no lack of proper female characteristics.

Embryologically, there are three materials which may be considered as containing masculinizing factors. First, in the gonads, there are two parts: the tubules and the interstitial cells; and second, as has been mentioned, the adrenal cortical material. The virilistic effects of the adrenal cortex have been explained as due to its proximity in origin to the gonadal anlagen. Such an explanation is, however, quite obscure and inadequate. A functional linkage between gonad and adrenal cortex, although elusive so far, is strongly suggested. In the normal ovaries used in this study, adrenal cortex is absent.

DR. McCAHEY (closing).—With regard to what has been said about removal of tumors of the adrenal without beneficial results, it is quite possible that, in such instances, the virilism persists because of endocrine activity of testis tissue in the ovary. It is also conceivable that removal of an ovarian tumor would not completely relieve virilism and the reason might be that testis tissue in the mesovarium was left behind.

I must disagree with Dr. Mazer's statements. There is abundant experimental evidence that testis hormone causes masculinization. For example, the ordinary barnyard hen has a functioning ovary and a rudimentary ovary. If the good ovary is removed the rudimentary ovary may develop into a testis-like organ. This is due to growth of tissue representative of the primary gonad in the ovary. The bird will then develop all the characteristics of a rooster but is, nevertheless, genetically a female. In a recent issue of *Endocrinology* an experiment was reported in which it was found that implantation of ovaries into the ears of castrated male mice prevented the atrophy of the prostate and seminal vesicles which invariably follows castration. It seems likely that the explanation of this finding is that the implantation of the ovaries into the particular site chosen, which would have a temperature comparable to that of the scrotum, permitted the testis remnants in the ovary to remain active.

Dr. Mazer also states that he finds that when he injects large amounts of testis hormone into women they do not develop virilism. I would like to point out that similar injections into men with the symptoms of hypogonadism have practically no effect. It appears that the commercial preparations of testis hormone at present available are not potent therapeutically.

In his discussion Dr. Mazer said repeatedly that it was not possible to use more than one or two animals in the urinary assays for testis hormone. It is our practice to use three or more birds for each assay. We have never reported a finding based on the result obtained in one capon. A few of our assays are based on the response obtained in two capons but such were due to the fact that one of the trio originally injected was found to be unsatisfactory for test purposes.

AN EVALUATION OF THE ANTERIOR PITUITARY-LIKE SUBSTANCE INTRADERMAL TEST FOR PREGNANCY

With a Study of the Possible Relation of This Test to Prolan Content

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VERY soon after Gilfillen and Gregg[1] described their "new, rapid, economical test for pregnancy and gynecological conditions," this study was undertaken. That this test is not entirely new has already been pointed out by the *Journal of the American Medical Association*.[2] The test was first proposed in 1929 by Porges and Pollatschek[3] of Vienna who subsequently reported the test as not wholly reliable. Alfred Deutsch[4] in 1929 and Hyman Strauss[5] in 1930 also reported the test as unreliable after their investigations. Weisman and Yerbury[6] recently came to the same conclusion. Huberman, Israeloff and Hymowitz[7] reported in their paper read at the American Medical Association Convention in Atlantic City in June, 1937, that the test was accurate in 95 per cent of the pregnant women. They used "follutein" as an antigen in performing the intradermal test. They do not offer this test as a substitute for other tests but as a simple aid in the diagnosis of the gravid state. Schneider and A. E. Cohen,[8] however, concluded that the results obtained with antuitrin-S injected intradermally in no way exhibit the reliability of this test as a means of diagnosing pregnancy or gynecologic disorders. The present authors' controlled studies upon a large group of patients completely justify the statement in the *Journal of the American Medical Association,* "There is, as yet, no reason to believe that the test is any more reliable now than it was in 1929."

The test as performed by Gilfillen and Gregg was duplicated exactly. This consisted of the intradermal injection of two minims of fresh anterior pituitary-like substance from pregnancy urine which had been kept on ice. Readings were taken at the end of one-half hour and at the end of one hour. A failure of the skin to react was read as positive for pregnancy. An increase in the size of the wheal above 7 mm. in diameter with a surrounding erythema was read as negative for pregnancy. The test material used had an "expiration" date that was a minimum of four to five months after its use.

Eighty-eight pregnant women were used in the first part of the study. These women all attended the Prenatal Out-Patient Clinic of the Coney Island Hospital and were pregnant two or more months. Table I summarizes the readings and results in this group.

Of these 88 women, 8 gave a nonpregnancy reading; 80 gave a pregnancy reading.

In the second part of the study 41 women were used. These included patients on the wards of the hospital and female technicians in the laboratory. One of these

TABLE I. RESULTS OF SKIN TESTS IN PREGNANT WOMEN

NUMBER OF CASES	LENGTH OF PREGNANCY IN MONTHS	NUMBER OF PREGNANCY REACTIONS	NUMBER OF NONPREGNANCY REACTIONS
6	2	4	2
6	3	6	0
18	4	16	2
12	5	12	0
15	6	13	2
17	7	16	1
11	8	10	1
3	9	3	0

women was admitted to the hospital for a threatened abortion. She was approximately fifteen weeks pregnant and was expected to give a positive pregnancy reading but did not. After several days in bed, she was discharged as still pregnant. Of the remaining 40 women, 27 gave a positive pregnancy reading; 13 gave a negative pregnancy reading.

During pregnancy the prolan content of the body increases. The findings of an increased prolan in the female may mean pregnancy. In view of the unexpected high number of positive pregnancy readings obtained in the nonpregnant group of women, it was decided to study the possible relationship of these findings to prolan content.

Ten nonpregnant women who gave a definitely positive pregnancy reading were selected for prolan determinations. These determinations were done using a modification of Zondek's method for the extraction and assay of follicle stimulating hormone (Prolan "A") from the urine.[9] Microscopic examinations of the ovaries from the autopsied mice was done in all cases as a check on the gross diagnosis of positive or negative prolan. Of the 10 women selected for these prolan studies, all showed negative prolan readings, indicating no increase in their prolan excretions in the urine.

TABLE II. PROLAN STUDIES IN NONPREGNANT WOMEN AND IN MEN WITH POSITIVE SKIN TESTS

	NO. STUDIED FOR PROLAN	PROLAN NEGATIVE	PROLAN POSITIVE
Nonpregnant women with positive pregnancy skin test	10	10	0
Men with positive pregnancy skin test	6	5	1

Increased prolan may be found in such conditions as early menopause, hyperthyroidism, incomplete abortion, chorioepithelioma, follicular cystosis of the ovary, persistent corpus luteum cyst of the ovary, testicular atrophy, removal of the testicles, over-secretion of the pituitary gland as in gigantism, acromegaly, etc., pregnancy, and following bilateral oophorectomy. If any of these conditions were present they were not marked by an increased prolan. The mechanism of this "intradermal test for pregnancy" is not entirely clear. It does not seem to be related to either pregnancy or to prolan content of the body.

Seven women in whom prolan determinations revealed a positive or increased amount of prolan in the urine were skin tested. Five of these showed no reaction. Two showed a wheal and erythema indicative of a nonpregnancy. These findings show that as a test for prolan in the body the intradermal injection of pituitary-like substance is of no value. In 15 nonpregnant women who showed positive pregnancy skin readings only 5 had positive prolans, whereas 2 women with a positive urinary prolan gave a negative pregnancy skin reading.

In the third part of this study, 33 men were tested.

These included physicians, laboratory technicians and workers and patients on the wards of the hospital. Of these 33 men, 8 gave a nonpregnancy reading; 25 gave a positive pregnancy reading. Six of the men who gave positive pregnancy readings were further studied for their prolan content. Five of these prolan studies were negative, indicating no increase in their prolan excretion in the urine. One man, 55 years of age, showed a positive prolan.

TABLE III. SUMMARY OF SKIN TESTS IN PREGNANT WOMEN, NONPREGNANT WOMEN AND IN MEN

		NO. OF PREGNANCY REACTIONS	NO. OF NONPREGNANCY REACTIONS
Number of pregnant women	88	80	8
Number of nonpregnant women	40	27	13
Number of men	33	25	8
Total number of cases studied	161		

SUMMARY

1. The intradermal administration of anterior pituitary-like substance of pregnancy urine as a diagnostic test for pregnancy shows the following deviations from expected results on proved cases:

a. Of expected positive results in 88 pregnant women there were 8 who gave negative results.

b. Of expected negative results in 40 nonpregnant women, only 13 gave a negative pregnancy reading, 27 were positive for pregnancy.

c. Of expected negative results in 33 men, 8 showed the expected result, 25 showed positive pregnancy tests.

2. Prolan studies done on 10 nonpregnant women who gave a definitely positive pregnancy reading were negative.

3. Prolan studies done on six men who gave a definitely positive pregnancy reading were negative in 5 and positive in 1.

4. Of 7 nonpregnant women with a positive prolan, 5 gave a positive pregnancy test and 2 a negative test.

5. The results are in substantial agreement with other recent critical analyses of this diagnostic procedure.

The authors wish to thank Dr. D. A. McAteer, Director of the Surgical Service, and Dr. H. B. Matthews, Director of the Obstetrical Service, for their cooperation.

The authors also wish to thank Dr. Charles H. Birnberg for his kind suggestions during this study.

The Anterior-Pituitary-like substance used was antuitrin-S (Parke-Davis & Co.).

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UTERINE BLEEDING WITH VIRILISM*

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THIS patient, a 21-year-old, colored, single female, illustrates an unusual type of uterine bleeding. She began to flow at thirteen and had a normal menstrual cycle thereafter. During her eighteenth year she noticed an incipient growth of hair on her chin, cheeks, and upper lip. Soon her menstrual periods became increasingly more abundant, and the interval between the bleeding grew shorter. She was chronically tired, had vertigo, anorexia, and her psychic condition was far from serene with the consciousness of her unfeminine appearance. She gave up her job and, aside from her visits to several physicians, remained secluded. By the autumn of 1936 the hypertrichosis required shaving every other day, and the bleeding was severe, occasionally lasting as long as a month, with irregular short intervals.

Various physicians consulted seemed to have presumed that she had committed an abortion, and she was apparently treated on that hypothesis, or on the basis of a mild pelvic inflammation. In October, 1936, she had a transfusion. When she was admitted to the Gynecological Service of the Woman's Hospital of Philadelphia, Jan. 4, 1937, the patient was not acutely ill, although she had bled most of the month previously. Her hemoglobin was 52 per cent Dare, R. B. C. 2,610,000, W. B. C. 15,000, polymorphonuclear leucocytes 78 per cent, lymphocytes 22 per cent, blood sedimentation time 155 minutes, temperature 98.4°, pulse 96, and respiration 20.

A physical examination revealed no deviation from the normal, except a slightly low blood pressure, hypertrichosis, and pallor. Her voice was contralto. The pelvic examination disclosed no signs of inflammation. The clitoris protruded sufficiently to separate the labia majora and measured 3.75 cm. long by 0.75 cm. diameter. Aside from size it was not abnormal. The vaginal introitus was intact. The cervical os easily admitted a cotton applicator, and the cervix was soft, pink, intact, and mobile. The fundus was slightly enlarged, soft, smooth, mobile, anterior, and tender. In the right and left fornices were two discrete, firm, ovoid masses about 5 by 3 by 2 cm. in size.

The following day a diagnostic curettage of the uterus was performed. The uterine cavity measured 7.5 cm. and abundant, thick, soft, irregular scrapings were secured.

Dr. Berta Meine, Pathologist, examined the scrapings and believing that the diagnosis lay between severe hyperplasia of the endometrium and adenocarcinoma, and feeling the situation too precarious to risk a final diagnosis, returned the pathologic report as adenocarcinoma.

The patient was given a blood transfusion and on Jan. 13, 1937, Dr. Fetterman performed a panhysterectomy with a bilateral salpingo-oophorectomy. No radiation was given. The patient made a rapid uneventful convalescence, and has been well since. There has been no diminution of the hypertrichosis and size of clitoris. Basal metabolic rate tests have not fluctuated more than four points from plus 16.

*Read at a meeting of the Obstetrical Society of Philadelphia, October 7, 1937.

X-rays of the skull have demonstrated an apparently normal sella turcica with no evidence of pituitary abnormality. Roentgen studies made prior to the second operation to discover any metastases failed to disclose any evidence of osteoporosis and an intravenous urogram presented a picture of a normal urinary tract, without any displacement of the kidneys by suprarenal glands. The patient refused air injections in the renal region designed to indicate the presence of an adrenal neoplasm. At no time have hormone assays been made owing to lack of resources and later the reluctance of the patient.

The photograph (Fig. 1) of the specimen was taken within one hour of operation and shows the normal-sized uterus and tubes, and the enlarged microcystic ovaries. On section of both ovaries, we discovered an area above each hilum that was grayish orange, slightly softer than the remainder of the tissue. Aside from these yellowish places, the ovaries did not differ greatly from the firm, thick tunica microcystic ovaries we have found so frequently accompanying hyperplasia of the estrin type.

Careful microscopic sections through each entire ovary appeared almost identical (Figs. 2 and 3). The ovaries showed follicles in all stages of normal development

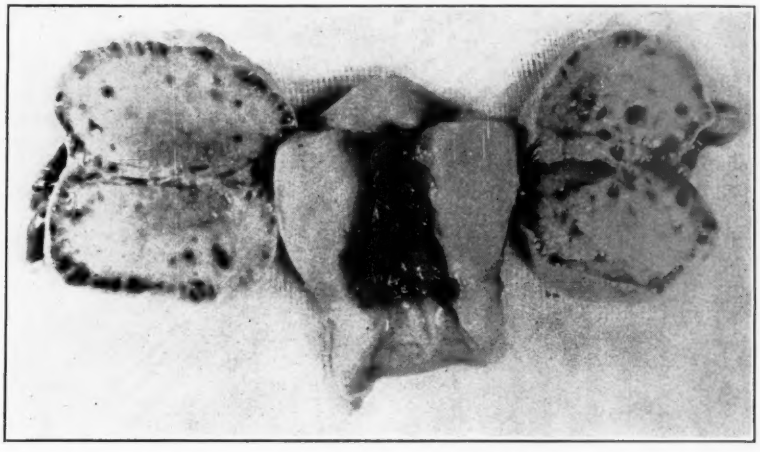

Fig. 1.—Photograph taken by M. Cousens of uterus, tubes, and ovaries immediately after operation.

and the periphery of each ovary was set with multiple small follicular retention cysts covered by a thick fibrous tunic. There was but one corpus album and no corpora lutea. In the areas of the yellow-gray substance there were definite structures unusual to ovaries. Surrounded by a fairly thick mass of cells (that closely resembled theca lutein cells) was an area about the size of a Graafian follicle in middevelopment, in which there were wisps of connective tissue and what might have been small fat cells. This core of tissue faintly suggested the texture of a fibroma ovarii. But it was very different from the fibroma ovarii, for there the thin spidery tissue was diffuse, while in these ovaries the thin bits of tissue formed the core of a definite structure pattern, repeated often in either ovary. Occasionally one saw a thin walled blood vessel in the core, but no sign of hemorrhage. These structures appeared only in the area where grossly the yellow tissue was apparent. In no way did they suggest adrenal tissue.

We have been unable to make a satisfactory diagnosis—many questions require answers first. Are the endometrial scrapings those of severe estrin type of hyperplasia associated with multiple follicular retention cysts, or are they adenocarcinoma? There was no evidence of cell invasion.

Uterine bleeding of hyperplasia endometrii is not usually seen in women having hypertrichosis and macroclitoris. Moreover hypertrichosis and an enlarged clitoris are almost invariably associated with scanty periods, generally with amenorrhea. In

a search of literature I have found no case in which virilism and such profuse bleeding were concomitant.

It is possible that there be an hypertrophy of Grollman's androgenic layer of the adrenal sufficient to cause masculinization without causing an enlargement of the adrenal bodies great enough to detect its presence this side of an adrenal biopsy. However, such hypertrophy is usually accompanied by a marked and rapid increase of weight. Our patient had little weight change aside from the loss of a few pounds which she regained postoperatively. Basophilic adenoma of the pituitary is accompanied by hypertrichosis and sometimes clitoral hypertrophy, but the skin striae, the hypertension, the osteoporosis, and the obesity, also of Cushing's syndrome, are absent in our patient.

Perhaps the pituitary condition, which is believed to stimulate the formation of multiple follicles, also stimulates the androgenic tissue of the adrenals, each hormonal influence being sufficiently strong to maintain its specific effect. Yet we are used to thinking of the male or female factor as dominant; even in hermaphrodites one type of secondary sex characteristics rules.

Fig. 2.

Fig. 3.

Fig. 2.—Low-power of ovary showing a definite attempt toward the formation of a structure. Three such places are visible. The one marked with the arrow is the entity selected for the high power microphotograph in Fig. 3.

Fig. 3.—High power of wall of peculiar area seen in Fig. 2.

Still remains the problem of the structures seen in the yellowish part of the ovaries. Perhaps the theca lutein-like cells impart the yellow color. We have no experience with xanthrofibroma folliculare which W. Schiller mentioned in the December, 1936, number of the *Journal of Obstetrics and Gynaecology of the British Empire*. He speaks of it as an unripe cellular fibroma, varying from the size of a hazelnut to a fist, permeated by small lipoid droplets and says that clinically it causes mechanical symptoms of fibroma, yet the fat which it produces and stores has an hormonic character which may at times cause hyperplasia of the mucosa and bleeding. He furthermore notes amenorrhea can also occur, because the elements of the tumor are luteinized connective tissue of the ovary. We have been unable to find further references, and we can only see faint resemblance to this entity in the peculiar structures of these ovaries. Nevertheless, one does not forget the close relation of the chemical structure of sterols and the sex hormones.

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ARSENICAL ENCEPHALITIS DURING PREGNANCY

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A RARE but often fatal reaction resulting from arsphenamine administration in the treatment of syphilis in pregnancy is hemorrhagic encephalitis.

A review of the literature from 1912 to 1937 showed this condition to be fatal in 29 pregnant women. In a series of 17,000 arsphenamine injections given at the University of Pennsylvania Hospital, the only death reported occurred in pregnancy. During the ten years prior to 1927, Kristjansen of the Rudolph Beegh's Venerological Hospital in Copenhagen reported three deaths in pregnant women. In our obstetric service, which handles approximately 1500 cases a year, only two cases of hemorrhagic encephalitis following arsenical administration have recently occurred. We wish to report these two cases.

CASE 1.—M. M., a 34-year-old white female, was admitted to the hospital in June, 1937, with the symptoms of dyspnea, dizziness, and inability to walk. There was a red macular rash over the entire body. Previous to admission she had received neoarsphenamine injections for syphilis at the Dispensary. Nine days before the onset of her symptoms she had received her first injection of the drug. Her past history revealed the usual childhood diseases. She had had six pregnancies, of which the first five were normal full-term deliveries. All five children are living and well. Her sixth pregnancy was a one and one-half month abortion induced by the patient with ergot. At the onset of her present illness the patient was approximately eight months pregnant. The course of the present pregnancy had been normal, and the estimated date of confinement was July 12, 1937. A routine examination of the blood at the Dispensary gave a positive Wassermann reaction, and the patient was advised to submit to antisyphilitic therapy.

The physical examination revealed a well-developed, well-nourished white female with audible inspiratory and expiratory dyspnea. The tongue was markedly swollen. Her pupils were round and equal and reacted to light. No nystagmus was noted. The examination of the heart and lungs revealed no pathology. The abdomen presented the aspect of an approximately eight-month pregnancy. The position of the fetus was back to the left and occiput anterior and a cephalic presentation. The fetal heart sounds could be heard but the rate was not determined. The patient showed a red macular rash over the extremities and abdomen. The biceps, triceps, and patellar reflexes were exaggerated. The Gordon, Oppenheim, and Babinski reflexes were positive.

Laboratory Findings.—The Wassermann reaction, which had been positive when examined at the antepartum clinic, was negative in the hospital. The hemoglobin content was 14.6 gm.; the red blood cells numbered 3,900,000; the white blood cells numbered 13,250. The differential count showed 70 per cent segmented polymorphonuclear leucocytes and 16 per cent were immature leucocytes; 6 per cent were lymphocytes; 4 per cent were monocytes and 4 per cent myelocytes. The number of platelets was 296,400. The urine was 1.040, acid, albumin content 20 mg. per cent, and a positive reaction for sugar and acetone. Microscopically a moderate amount of red blood cells, numerous white blood cells, and hyaline, granular, and cellular casts were noticed. The spinal fluid showed on her third hospital day an increased pressure of 140 to 200 mm. of water. On her fourth hospital day the pressure rose to 340 mm. of water. The spinal fluid was clear, the cell count was not increased; there was a positive globulin reaction and the colloidal gold curve was normal. The Wassermann and Kahn reactions were negative.

On admission the patient was restless but rational. Her respirations were stertorous, her tongue thick, and her pulse was rapid and of poor volume. She had involuntary micturition. During the following day her temperature rose and the pulse rate increased to 140. The rate of the respiration was 40. During the night swallowing became difficult and the respirations were labored and shallow. The patient at this time refused anything by mouth. On the third day muscle twitching could be noticed in the extremities. The patient at this time was in a deep coma, her temperature rose to 103.7° F., and she was perspiring profusely. Due to her inability to swallow, a large amount of mucus then accumulated in the mouth and made the use of a suction apparatus necessary. At this time no more fetal heart sounds could be heard, which indicated death of the fetus. On the fourth day the patient roused for a short period from her coma, but her pulse rate and temperature rose to 105.8° F., and cyanosis began to become manifest. Towards the same evening she developed Cheyne-Stokes type of respirations. Her pulse became rapid, weak, and irregular, and she died the afternoon of the same day.

During her six days of illness our therapeutic efforts consisted chiefly in the administration of sodium thiosulfate, various sedatives, heart stimulants, and the parenteral administration of saline, sucrose, and magnesium sulfate.

Summarizing briefly the important features of the above history, we may state that the patient apparently developed an acute and very progressive lesion involving chiefly the respiratory center in the medulla oblongata causing death by respiratory paralysis. While no definite localizing brain symptoms were present at any time, the severe coma, the involuntary micturition, incoherent moving of the extremities with clonic contractions of the muscles and increased reflexes pointed definitely to extensive involvement of the brain. The albumin in the urine in the absence of acute congestion can be taken as evidence of toxic damage to the kidney parenchyma, and the appearance of the macular rash at the onset of the disease led us to establish the clinical diagnosis of acute arsenical intoxication following administration of neoarsphenamine.

CASE 2.—B. H., a 24-year-old white female, admitted to the hospital in July, 1937, with the symptoms of inability to speak, inability to breathe properly, vomiting, and sore mouth. Previous to admission she had been receiving neoarsphenamine injections for syphilis. Seventeen, ten, and three days before admission she had received her first three injections of the drug. The day before her last injection she had complained of nausea and had vomited twice during the same day. The day of her last injection she was nauseated and vomited persistently since the time of injection. During the evening of the same day she first noticed difficulty in speaking.

Her past history revealed the usual childhood diseases. She had had three pregnancies, of which the first was a miscarriage, the last two normal full-term pregnancies. Both children are living and well.

At the time of her present illness the patient was approximately eight months pregnant. The course of this pregnancy had been normal and the estimated date of confinement was August, 1937. The Wassermann reaction of her blood was strongly positive, and antisyphilitic treatment was started at the dispensary.

The physical examination revealed a well-developed and well-nourished white female with audible inspiratory and expiratory dyspnea. The expiratory rate was 30 per minute. There was a definite lateral nystagmus present. The pupils were unequal in size but did react to light and accommodation. There was a severe pallor around the nose and mouth. Upon inspiration the nostrils were drawn into the septum. The breathing was harsh and loud and the auxiliary respiratory muscles had to be used by the patient to get sufficient air. The mucous membrane of the mouth was pale and the tongue was heavily coated. The breath was foul. There were uncontrolled movements of the arms and legs. No clonic or tonic contractions were present. The patient seemed dazed and could not answer questions; however, occasionally she would indicate answers with her fingers. The examination of the heart and lungs revealed no pathology. The abdomen presented on examination an approximate eight months' pregnancy. The position of the fetus was back

to the right and occiput anterior and a cephalic presentation. The fetal heart sounds could be heard in the lower right quadrant, and the rate was 140. The patient was not in labor. The rectal examination revealed the fetal head well above the rim of the pelvis, and there was no dilatation of the cervix present. The biceps, triceps, and patellar reflexes were increased. The Babinski, Gordon, and Oppenheim reflexes were positive. Ankle clonus was not present; neither was the Chaustek's nor Trousseau's sign present. There seemed to be a spastic type of paralysis of the upper extremities. The forearms were flexed upon the arm and could be straightened out only with the greatest difficulty. It was impossible to perform any laboratory work on this patient due to the rapid and fatal course of the disease.

On admission the patient was excited and restless and could not speak. Her respirations were stertorous and labored, and her pulse rapid but of poor volume. There was profuse diaphoresis present; her skin was cold and clammy. Her blood pressure at this time was 100/70, and the fetal heart sounds were 140. Later during the night the patient's finger nails, ear lobes, and lips became cyanotic. An acute laryngeal edema seemed to develop, and an emergency tracheotomy was performed.

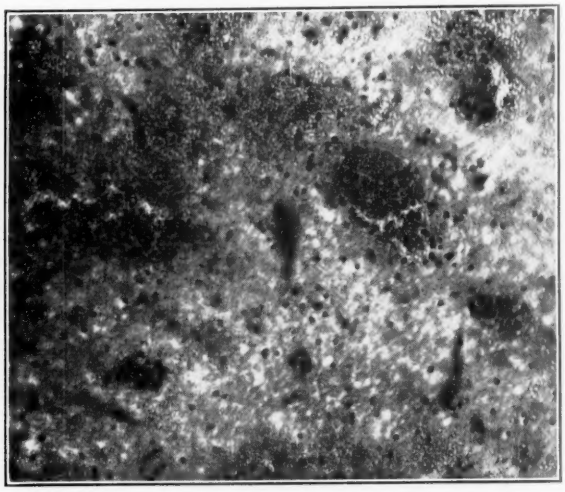

Fig. 1.—Microscopic picture of the hemorrhagic encephalitis. (Haem.-eosin ×120.)

After the operation the respirations seemed less labored. The pulse had increased to 128 beats per minute; the volume was still poor. A large amount of mucus accumulated in the mouth due to her inability to swallow, and made the use of a suction apparatus necessary. At this time the patient was in deep coma. Her temperature rose to 105.6° F. At this time fetal heart sounds were still audible and the rate was 140. The patient's condition remained the same during the night until early in the morning, at which time the respirations became rapid and shallow, the pulse weak and irregular, and the temperature rose to 107.8° F. Soon the pulse became faster and the patient died under gasping respirations and deep cyanosis. A postmortem cesarean section was done immediately, and a normally developed stillborn baby was delivered.

Our therapeutic effort during her brief illness consisted chiefly in the administration of various sedatives, heart stimulants, oxygen, emergency tracheotomy, and sponge baths.

Summarizing briefly the important features of the above history, we may state that the patient apparently developed an acute and rapidly progressive lesion in the medulla oblongata, causing death by respiratory paralysis. The severe coma, the lateral nystagmus, the increased reflexes and positive signs, incoherent moving of the extremities with clonic contractions of the muscles pointed definitely to diffuse

involvement of the brain. The symptoms, history, and physical findings, and the fact that one previous case had similar findings suggested to us the clinical diagnosis of acute arsenical intoxication following administration of neoarsphenamine. The autopsy findings confirmed our clinical diagnosis.

The detailed pathologic description of the cranial cavity and its contents is as follows: The superficial aspects of the cerebral hemispheres presented a marked congestion, a slight thickening of the meninges along the vessels, and a moderate softness of the brain substance. The consistency was apparently the same in both cerebral hemispheres. The spinal fluid was slightly blood-tinged, and there was slight congestion of the walls of the lateral ventricles. There was marked congestion of the white matter of the brain and a few petechial hemorrhages were present. On cut section the pons revealed a marked softening and swelling with numerous small, discrete and confluent petechiae involving the entire cross section of the pons. The pathologic evidence found in the pons and the immediate surrounding structures presented a general aspect of hemorrhagic myelitis, probably of the arsenical type. Multiple sections through the brain stem revealed no involvement of the medulla or cervical cord. There were, however, bilateral areas of softening and diffuse pink staining of the thalamus bilaterally.

From these pathologic findings the anatomic diagnosis of acute hemorrhagic encephalo-myelitis was made. Other pathologic findings at the autopsy table included a slight atheromatosis of the aorta, fatty changes of the myocardium, parenchymatous degeneration of the liver and kidneys, dilatation of the ureter, chronic pelvic peritonitis with adhesions, and a slight anemia.

The histopathologic examination of various sections of the brain showed small petechial hemorrhages scattered throughout the entire brain but being most remarkable in the pons. There extensive destruction of the nerve substance by confluent and profuse hemorrhages could be noted. The vessels of the brain showed dilatation with hyperemia. The Virchow-Robin spaces were filled with blood which penetrated in the form of fine streaks into the surrounding nervous tissue. No infiltration with leucocytes could be noted. The ganglion cells of the cortex of the brain appeared slightly swollen with deep purple staining protoplasm.

CONCLUSIONS

A more constant supervision of the pregnant woman who is under arsphenamine therapy during the second and third trimesters is urged. The onset of hemorrhagic encephalitis is so insidious that the routine laboratory tests are of little diagnostic value. Constant questioning of the patient before each treatment in order to detect any evidence of early arsenical reaction may help to discover any toxic reaction to the drug.

A thorough history of the patient with reference to disease of the heart, kidneys, and lungs may call for special laboratory tests to check the function of these organs before the institution of arsenical therapy. Due to the rarity of this condition, it is not feasible to withhold arsphenamine treatment in pregnant syphilitic individuals.

Smaller doses of the arsenicals, given at weekly intervals, are indicated in the latter half of pregnancy. A constant check of the general health of the patient under treatment, with frequent examinations of the urine, appears to be the only means of preventing this serious treatment reaction in pregnant women.

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ACTINOMYCOSIS AND BLASTOMYCOSIS OF FEMALE GENITALIA

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IT IS a common belief that mycotic infections of the female pelvic organs are rare. To date 77 cases of actinomycosis have been recorded, the last by Lisa and Levine,[1] who gave references for all previously reported cases.

The only reports in recent years of blastomycosis affecting the female genitalia were by Ocana,[2] which affected the cervix uteri, and by Perazzi,[3] which was vulvovaginal in distribution. The latter can be considered comparable to cutaneous blastomycosis, which cases are common, next to which in occurrence are systemic and pulmonary cases. Single cases of blastomycosis affecting the urethra, kidney, bladder and prostate have been reported respectively by Preis and Foro,[4] Tepel,[5] Rhamy,[6] and Lewis, Carroll, and Stryker.[7]

The recent findings of a case of actinomycosis and another of blastomycosis are submitted as records to further the conception that mycotic infection of the female genitalia is probably more common than is realized.

ACTINOMYCOSIS

A. V., a young, white woman, aged 29 years, married and the mother of one child, born five years ago, was admitted to the hospital on Oct. 11, 1933, and gave the following history:

Shortly after the birth of this only child, she began to complain of pain in the right lower abdomen and was quite sick for several weeks in a hospital in Bayonne, N. J. At this time, she had a high temperature and for a time was "out of her mind." After recovering from this acute post partum period, she suffered continuously with pains in the right side, associated with nausea, vomiting, and poor appetite. The pains were always aggravated during menstruation. Her family history as well as her past history are entirely negative and have no bearing on her present illness. On examination, she appeared to be a well-nourished, young woman with good healthy color. The findings, aside from the lower abdomen were essentially negative. The abdomen revealed nothing above the umbilicus, but there was definite tenderness with some rigidity in the entire lower abdomen. Bimanual examination showed particularly marked tenderness in the right fornix and a definite palpable mass which was firm and adherent. A diagnosis of chronic pelvic inflammatory disease was made, apparently originating at the time of her delivery.

At operation on October 11, a right pararectus incision was made. The appendix was not immediately visible, but in the right pelvis a large, dense, adherent mass was found. It was closely fused with the uterus and a loop of the ileum. This was carefully separated and found to be the site of an old abscess with a mass about the size of an apple, involving the right tube and ovary and the right cornu of the uterus. All of this diseased tissue was completely excised. The left ovary was left in situ after puncturing a few small cysts. The appendix was small and atrophic, but surrounded by adhesions. It was removed. The abdomen was then closed with a cigarette drain to the pouch of Douglas.

Laboratory Findings.—Oct. 11, 1933. Urine normal except for a faint trace of albumin; W.B.C., 8,800; polymorphonuclear neutrophiles, 58 per cent; eosinophiles, 3 per cent; monocytes, 2 per cent; lymphocytes, 37 per cent. Culture from operative area shows pure growth of *Staphylococcus aureus.* Oct. 17, 1935. W.B.C., 19,650; polymorphonuclears 84 per cent; eosinophiles, 1 per cent; monocytes, 2 per cent; lymphocytes, 13 per cent.

Fig. 1.

Fig. 2.

Fig. 1.—Case 1. Actinomycotic mass in the Fallopian tube. Gram stain, showing marginal filaments gram-positive and central granular mass gram-negative. ×65.

Fig. 2.—Case 1. Margin of actinomycotic mass in the Fallopian tube, showing gram-positive filaments and granular center. ×700.

Pathologic Report.—Specimens consisted of right Fallopian tube and ovary together, the left tube and the appendix. Right tube measured 10 cm. in length and 2 cm. in greatest diameter. The distal end was closed. Serous surfaces were pale, dull, and smooth. Cut surfaces showed thick, pale, firm walls and large lumen filled with thick, creamy fluid. Right ovary measured 4 cm. in greatest diameter. It was oval in shape and externally encircled by the tube, which was firmly adherent to it. Cut surfaces showed pale, firm tissue with numerous small round cysts just beneath the exposed surfaces. Left tube measured 5 cm. in length and appeared normal. Fimbriated extremity was patent. Appendix measured 2.5 cm. in length and 0.3 cm. in almost uniform diameter. Cut surfaces showed pale firm structure and no evidence of a lumen.

Microscopic Examination.—The right Fallopian tube had the lumen distended and the walls thinned by the purulent contents, consisting mostly of polymorphonuclear leucocytes but with a high proportion of plasma cells and less so of lymphocytes, among which were found small masses of actinomyces (Figs. 1 and 2). Many of the strands of muscle tissue in the walls were separated by collections of similar cells

but with plasma cells predominating. Between the tubal and ovarian structures were binding masses of fairly loose, newly formed fibrous tissue and the adjacent ovarian structure appeared unaffected. In other places the ovarian structure was affected by small areas being densely occupied by polymorphonuclear leucocytes and plasma cells, in about equal proportion. In none of these areas of the ovarian tissue were found any masses of actinomyces as observed in the tube. In the outer border of the affected tissues were extensive areas of newly formed fibrous tissue, into most of which were scattered many of the inflammatory cells. The vascularity showed but little increase.

The masses of actinomyces showed little morphologic structure in sections stained by hematoxylin and eosin, except for a few mycelial filaments projecting at the margin. By Gram stain the periphery had many intertwined gram-positive hyphae. The central portion was gram-negative and resembled a mass of densely packed amorphous granules, none of which showed any suggestion of a crystalline structure.

Appendix showed obliteration of the lumen and no evidence of any other pathologic change.

Her postoperative period represented a very normal convalescence for the first five days. The drainage was a dark serous material. On the fourth day, she felt nauseous and vomited. On the fifth day, her temperature began to rise, reaching a maximum of 104.6° F. on the seventh day and then gradually came down by lysis, returning to normal on the thirteenth day.

On the fifth day, she became irrational and was very drowsy. She had periods of excitation and hyperactivity and had to be restrained. On the eighth day, she had a fine reddish rash on her chest and arms suggesting a bromide rash. Also, there was some purulent discharge from the wound.

After thirteen days, her mental condition returned to normal, the wound cleared and she made an excellent recovery. The mental disturbance, according to her husband, was similar to the one she suffered following the birth of her child.

This patient was followed for six months after the operation, since when it has been impossible to locate her. For the time observed, she enjoyed excellent health.

BLASTOMYCOSIS

M. P., a young, white woman, aged 29 years, was admitted to the hospital on Jan. 16, 1934, with the following history:

For the past four years, she had had pelvic pain, bearing down, numbness in the right leg with headache, indigestion, and backache. She never had leucorrhea. Lately, she had some nausea, vomiting and chronic constipation. She was married at the age of 18 years, living with her husband for one year. She married the second time a man about ten years older than herself and lived with him for three years. Her menses appeared every five to six weeks, lasting ten days. Occasionally, she had a period in between, but the flow was usually scant. Physically, the patient appeared well-nourished and of good color. Examination was essentially negative, except that on vaginal examination there was revealed a large, nodular, immovable uterus, suggesting multiple fibroids.

Operation on Jan. 17, 1934, through a midline incision, revealed a mass consisting of the left tube and ovary, surrounded by the rectum. The right tube was behind the uterus, about the size of a lemon. The appendix was apparently adherent and involved in the mass on the right side, between the tube and the cecum.

The left tube and ovary were removed en masse. The right tube and apparently the remnant of the appendix, were also removed. The numerous adhesions were separated and after suturing the fundus of the uterus to the peritoneum, a cigarette drain was placed in the pouch of Douglas and the abdomen was closed.

Laboratory Findings.—Urine was negative except for very faint trace of albumin. Culture from operative area; no bacteria.

Pathologic Examination.—Specimens consisted of right tube and left tube and ovary. Right tube measured 7 cm. by 3 cm. by 2 cm. External surfaces are pale and dull. Cut surfaces showed thick, firm, pale walls and lumen slightly distended with thick, creamy fluid. The distal end was closed. Left tube and ovary appeared fused together into a single large mass, measuring 6 cm. by 5 cm. by 4 cm. External

surfaces were dark red and rough. Cut surfaces showed thick, firm, pale walls, and the lumen was distended and closed off into several cystic cavities filled with thick, creamy fluid.

Microscopic Examination.—Both tubes were densely filled with polymorphonuclear leucocytes and almost as many plasma cells. These same cells extended into the walls between the strands of muscle. Beyond these the ovarian tissue was attached by extensive fibrous tissue in which were many plasma cells, some lymphocytes and a few polymorphonuclear leucocytes. The surrounding ovarian stroma showed considerable increase in dense fibrous tissue. In the tissue from the right side it was impossible to identify any portion of the appendix. Direct examination of unstained contents of the tubes showed the presence of some budding yeast cells. Inoculation upon Sabouraud's media shows growth of budding yeast cells and also mycelia with arthrospores and conidia (Fig. 3). Subcultures give variations in appearances of the colonies with considerable tendency to early pleomorphism. All the colonies present a tough, dark brown, leathery mass, which is also a distinctive characteristic of blastomyces.

Her postoperative course was uneventful. She made an excellent recovery and was discharged from the hospital on Feb. 3, 1934, and has enjoyed fine health to the time last seen which was in September, 1936.

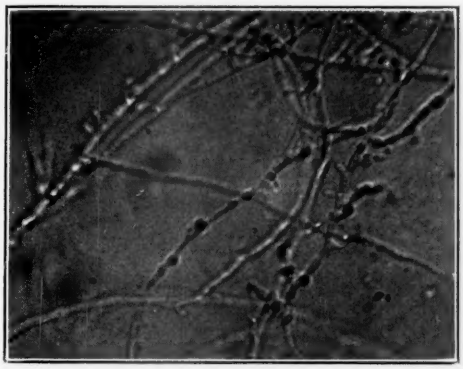

Fig. 3.—Case 2. Blastomyces cultured from budding yeast cells found in pyosalpinx. Unstained. ×700.

DISCUSSION

Most cases of mycotic infection of the female genitalia have been reported originating by extension from the gastrointestinal tract. In the actinomycosis case there is nothing to support such an origin, and it can be considered to have occurred by way of the genital tract following delivery, as in the case cited by Junghans.[8] The blastomycosis case evidently occurred by extension from the appendix to the right tube and ovary between which there was such a massive lesion that the appendix as part of the tissue removed was not recognized.

The 71 cases of actinomycosis of female genitalia listed by Cornell[9] were classified as follows: cured 11, improved 8, doubtful 7, died 45. To this may be added three cured cases: Gardiner,[10] Lisa and Levine,[1] and the one herein cited; and three fatal cases, two of Counsellor and Hoerner,[12] and one of Junghans.[8]

The two types of fungi here cited are widely different from each other in their characteristics. Their classification among the other fungi is given by Castellani[13] and Henrici[14] who state the actinomyces as being closely related to the mycobacteriaceae and bacteria, especially the acid fast types. Both classify the other organism, blastomyces, under the fungi imperfecti and Castellani[15] applies the name blastomycoides to it, discarding the term blastomyces and using that of blastomycosis for the yeasts (saccharomyces) and the three yeastlike organisms (cryptococcus, or torula, monilia and endomyces).

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A FIVE-YEAR STUDY OF ECLAMPSIA IN MARYLAND

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IT HAS often been reported that the incidence of eclampsia in the State of Maryland is unusually high. These reports were principally based upon the work of Williams[1] in 1912. This study has been undertaken to find if this assumption is still justified, and at the same time to investigate other aspects regarding the disease in this State.

Medical literature provides considerable data on eclampsia. There are wide variations in incidence and mortality throughout the world. In the United States both incidence and mortality are about the average; however, it is estimated[2] that today eclampsia and the toxemia associated with it accounts for 30 per cent of the approximately 15,000 annual maternal deaths in this country. Therefore, as Bill[3] states, eclampsia still remains our greatest problem in obstetrics.

Table I gives a brief statistical review of eclampsia in various regions of the world. It is mostly based upon hospitalization rather than on the total number of births occurring in the given area, and probably accounts for the wide variation.

Our period of study includes the five years from 1931 through 1935. It is difficult to obtain complete information about eclampsia in Maryland as no report of the disease is made to the Health Department except when death occurs. As most cases of eclampsia in Maryland are hospitalized, it was felt that by examining the records of all hospitals in this state we could obtain nearly the complete incidence of eclampsia which occurred in pregnancies for the period. A questionnaire was made up and sent to each of the 34 hospitals taking care of maternity cases. One of the authors personally visited 14 of these hospitals and examined their records, while 18 others responded satisfactorily to the questionnaire. Two small hospitals in outlying sparsely settled districts failed to respond; however, it is our impres-

TABLE I. RÉSUMÉ OF CASES REVIEWED IN LITERATURE*

YEAR	AUTHOR	REGION	NUMBER OF LABORS	NUMBER OF CASES	% INCIDENCES	% PRIMIGRAVIDA	% MULTIGRAVIDA	% ANTE PARTUM	% INTRA PARTUM	% POST PARTUM	% MATERNAL MORTALITY	% FETAL MORTALITY
1912	Williams[1]	Baltimore	11,000	110	1.00	60.0	40.0	55.5	22.7	21.8	22.8	44.5
1922	McPherson[4]	New York	120,000	890	0.75	64.4	35.6	65.0	20.0	15.0	17.4	25.4
1922	Cruikshank[5]	Glasgow	23,630	814	3.44	65.1	34.9	------ 78.5 ------		21.5	22.4	36.6
1926	Greenhill[6]	Chicago	29,587	83	0.28	73.1	26.9	50.0	20.5	29.5	7.7	27.7
1926	Davis[7]	New York	152,248	879	0.57	N.R.	N.R.	58.0	13.4	28.6	23.0	34.0
1927	Rice[8]	New York	42,070	222	0.53	58.0	42.0	50.0	23.0	27.0	21.0	45.0
1930	Gyllensvärd[9]	Stockholm	48,053	282	0.60	N.R.	N.R.	N.R.	N.R.	N.R.	7.8	31.0
1930	King[10]	Peiping	2,256	33	1.50	75.0	25.0	60.0	30.0	10.0	12.1	44.0
1930	Upshaw[11]	Georgia	9,730	152	1.50	68.0	32.0	------ 84.0 ------		16.0	21.0	34.0
1930	Stapleton[12]	Calcutta	1,200	65	5.40	81.5	18.5	18.0	75.8	6.2	22.0	N.R.
1932	Hoffstrom[13]	Finland	25,260	240	0.95	80.0	20.0	N.R.	N.R.	N.R.	15.9	29.8
1932	Gerrard[14]	England	9,116	100	1.09	72.0	28.0	43.0	29.0	18.0	7.0	N.R.
1933	Gibson[15]	Australia	16,903	101	0.61	68.1	31.9	59.0	20.0	21.0	8.9	36.0
1934	Hauch[16]	Denmark	737,701	1,286	0.17	N.R.	N.R.	N.R.	N.R.	N.R.	15.5	34.1
1934	Binder[17]	New Jersey	18,942	123	0.70	N.R.	N.R.	31.7	31.7	36.6	11.4	44.3
1936	Kimbrough[18]	Philadelphia	12,601	43	0.34	80.0	20.0	65.2	9.8	25.0	13.9	28.0
1937	Reese and Peyton	Maryland	146,652	299	0.20	70.5	29.5	54.6	25.4	20.0	20.4	31.0

*N. R., Not reported.

sion that they do little or no obstetrics and their failures are relatively unimportant, affecting the final figures very little.

INCIDENCE FOR THE PERIOD OF STUDY

During the five-year period, 139,618 live births and 8,712 stillbirths were recorded in the State.[26] If correction is made for sets of twins (1,650) and triplets (914), the number of pregnancies represented by these births and stillbirths would be 146,652. Among these there were 299 cases of eclampsia or an incidence of 1 case in 490 pregnancies (0.20 per cent). Of the 299 cases, 69 occurred in 1931, 50 in 1932, 74 in 1933, 47 in 1934, and 59 in 1935. There is no significant variation in the number of cases appearing yearly.

PARITY

In the present series, 70.5 per cent were primigravidas and 29.5 per cent multigravidas (Table I). Of the 146,652 pregnancies, 46,428 were primigravidas and 100,224 were multigravidas. The incidence of eclampsia for primigravidas therefore, was one in 220 pregnancies or 0.45 per cent and for multigravidas one in 1,139 or 0.09 per cent. These results bear out the well-recognized fact that eclampsia is much more prevalent in the primigravidas.

RACE

The large negro population of Maryland made it possible for us to study the problem on a racial basis. One hundred and seven of the 33,155 colored pregnant women had eclampsia or one in 310 (0.32 per cent) as compared to one in 591 (0.17 per cent) in the white race. The prevalence of eclampsia in the negro is in agreement with the findings of Upshaw[11] in Georgia who reported an even greater incidence of 1.5 per cent, and it can partly be explained by the lack of prenatal care, age, and poor living conditions of these people. Table II gives a further comparison subdivided according to multiparous and primiparous pregnancies.

TABLE II. INCIDENCE OF PARITY BY RACE

	WHITE			COLORED		
	PREGNANCIES	CASES	INCIDENCE PER CENT	PREGNANCIES	CASES	INCIDENCE PER CENT
Primigravidas	37,724	136	0.36	8,704	75	0.86
Multigravidas	75,773	56	0.07	24,451	32	0.13
Total	113,497	192	0.17	33,155	107	0.32

TYPE OF ECLAMPSIA

One hundred and sixty-four or 54 per cent of the cases occurred ante partum, 75 or 25.4 per cent intra partum, and 60 or 20 per cent post partum. These figures coincide with most authors and very closely approximate the series studied by Williams.[1] The percentage of cases appearing ante partum and intra partum in the primigravidas and the multigravidas are about the same. Post partum eclampsia is 7 per cent more common in the multigravidas (Table III).

TABLE III. DIVISION OF CASES AS TO TYPE AND PARITY

	ANTE PARTUM		INTRA PARTUM		POST PARTUM	
	NO. OF CASES	PER CENT OF TOTAL	NO. OF CASES	PER CENT OF TOTAL	NO. OF CASES	PER CENT OF TOTAL
Primigravidas	118	55.8	55	26.0	38	18.2
Multigravidas	46	52.2	20	22.7	22	25.1
Combined	164	54.6	75	25.4	60	20.0

MULTIPLE PREGNANCY AND ECLAMPSIA

Crowe[19] and others[6, 11, 15, 18] report that from 4 to 7 per cent of their cases of eclampsia were associated with multiple pregnancy. In this series there were 9 multiple pregnancies or one out of every 30 (3 per cent), and since the normal incidence of twin pregnancy is usually given as one in 80, it could be assumed that eclampsia is 2½ times as prevalent here as in single pregnancies.

RECURRING ECLAMPSIA

In recent years more has been written about the recurrence of eclampsia. Peckham[20] reports that at Hopkins 4 per cent of all eclamptic patients suffer from a second attack in a future gestation; Young[21] in Edinburgh, cites various authors' findings as being from 1.5 to 2.8 per cent. Schmeckel finds that in Dresden 40 per cent of eclamptic patients have symptoms and 20 per cent develop convulsions in future pregnancies. The latter author states that in a recurring case the disease is benign. We found eclampsia recurring in 5 cases. Four of the cases were of the severe type and 3 patients died, making the mortality 60 per cent. We believe the physician should consider the pregnant woman with a history of eclampsia seriously. If a second attack has occurred, we recommend prevention of future pregnancies, and if she becomes gravid for the third time, and shows evidence of severe kidney dysfunction, we recommend abortion.

SEVERITY OF ECLAMPSIA

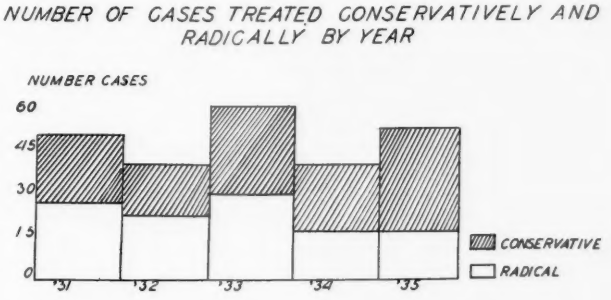
Each case of eclampsia was designated severe or mild depending upon the number of convulsions or coma. Ten or more convulsions or prolonged coma classified a case as severe. One hundred and nineteen or 40 per cent of all the cases were of the severe type, and ante-partum eclampsia appeared to be the most severe. The cases are compared according to severity and parity in Table IV.

TABLE IV. SEVERE AND MILD CASES ACCORDING TO PARITY AND TYPE

	ANTE PARTUM		INTRA PARTUM		POST PARTUM		TOTAL	
	SEVERE	MILD	SEVERE	MILD	SEVERE	MILD	SEVERE	MILD
Primigravidas	55	63	15	40	11	27	81	130
Multigravidas	23	23	4	16	11	11	38	50
Combined	78	86	19	56	22	38	119	180

TREATMENT

Probably no other obstetric complication has been given as much consideration as the handling of the eclamptic patient. There have been for the past twenty years two distinct schools of treatment: conservative and radical, the former gaining in followers as time goes on, and showing upon the whole decidedly better results for the mother, and apparently fairly good for the baby. The patients in



this study were treated in both ways, the conservative method increasing as time went on. So far as could be determined there were few, if any, variations from the accepted methods of sedation, rest, etc., in those cases so handled. One hundred and eight or 45.7 per cent of the 239 patients having ante- and intra-partum eclampsia were treated radically, the remaining 131 conservatively. Primigravidas were more often treated by hastening the termination of pregnancy than multigravidas, the percentages being 47 and 30 per cent, respectively.

In comparing Baltimore, the only large city in the State, with the rest of the state, an interesting finding was obtained. Table V shows the number of patients treated in Baltimore as compared to the rest of the state and the method of treatment for the patients having eclampsia before delivery. Twenty-seven per cent of the patients were treated radically in Baltimore in contrast to 65 per cent treated in the same way in the rest of the state.

TABLE V. TYPE OF TREATMENT BY LOCATION FOR ANTE- AND INTRA-PARTUM ECLAMPSIA

LOCATION	NO. OF CASES	TREATMENT	
		RADICAL	CONSERVATIVE
Outside of Baltimore	108	71	37
Baltimore	131	37	94

MATERNAL MORTALITY

Sixty-one of the 299 patients died giving a mortality of 20.4 per cent. This mortality rate is higher than in certain regions in the United States but is 10.5 per cent less than the report of 1912 for Baltimore.[1] The number of deaths in this study represent 8.3 per cent of the total 737 maternal deaths in the States for the period.[24] We have accounted for 61 of the 70 deaths reported as eclampsia on death certificates.

Forty-three or 71 per cent of the deaths were in the ante-partum eclamptic patients while 17 per cent and 12 per cent were in the intra- and post-partum cases, respectively. The mortality rates are shown in Table VI; post-partum eclampsia in multigravidas appear to be most fatal.

TABLE VI. MORTALITY RATES FOR THE CASES AS TO PARITY AND TYPE

GROUP	ANTE PARTUM	INTRA PARTUM	POST PARTUM	TOTAL
Primigravidas	24%	15%	2.7%	14%
Multigravidas	20%	12%	32%	28%
Combined	26%	13%	13%	20%

Surgical treatment increased the maternal mortality tremendously. Thirty-four per cent of all patients treated radically died, in contrast to 12 per cent

TABLE VII. REGIONAL MORTALITY OF CASES BY TREATMENT

LOCALITY	TREATMENT*					
	SURGICAL			MEDICAL		
	NO. CASES	NO. DEATHS	MORTALITY	NO. CASES	NO. DEATHS	MORTALITY
Outside of Baltimore	71	26	36%	40	7	27%
Baltimore	37	11	33%	91	9	10%
Maryland (Total)	108	37	34%	131	16	12%

*Post-partum eclampsia was not included in these figures.

mortality for those receiving conservative therapy. Table VII reveals the analysis of cases as to treatment in Baltimore and the rest of the State with their respective mortalities.

FETAL MORTALITY

Ninety-three of the 308 babies (includes 9 sets of twins) were stillborn or died within seventy-two hours. This gives a total fetal mortality of 30.2 per cent. Only two babies whose mothers had post-partum eclampsia died, giving a fetal mortality of 36 per cent for those patients developing eclampsia prior to delivery. This figure is much lower than the average for the world, and approximates the record of clinics reporting the lowest mortality rates. Prompt surgical treatment of the mother was followed by a 17 per cent fetal mortality, while those patients treated conservatively showed a 43 per cent fetal mortality indicating that the risk for the baby is considerably greater with medical therapy.

PRENATAL CARE

Prenatal care means considerably more than an occasional visit to a physician. There are many grades of care and only a small minority of patients receive adequate care. Grade 1 (a) as described in "Standards of Prenatal Care" (Children's Bureau Publication No. 153) is the desired type to give: This is described as follows:

"1. A careful history, medical, surgical, gynecologic, and obstetric; (2) a complete physical examination, including the examination of heart, lungs, and abdomen; (3) pelvic measurements, both internal and external; (4) the taking of blood for a Wassermann reaction; (5) minute instructions in the hygiene of pregnancy; and (6) visits to a physician at least once a month during the first six months, then oftener as indicated. The first visit must take place not later than the end of the second month. At each of the visits the patient's general condition is to be investigated: blood pressure, urinalysis, pulse, and temperature recorded; weight of the patient taken if possible; abdominal examination made, and the height of the fundus determined."

It was impossible in this series to determine the grade of prenatal care each patient received. One hundred and sixty-one or 54 per cent received no care whatsoever. The remaining 46 per cent made one or more visits to a physician. The care of the latter was far from adequate as determined in a detailed study of 50 of these 299 cases of eclampsia. Of this number only 5 patients received adequate prenatal care as prescribed above. Of the 128 patients noted as having received prenatal care, 8 died, giving a mortality of 0.7 per cent in contrast to a mortality of 33 per cent for those that received no prenatal care.

SUMMARY AND CONCLUSIONS

1. A general statistical study of eclampsia for a five-year period in the State of Maryland has been made.

2. A comparative table of eclampsia in various clinics and countries has been presented.

3. The incidence of eclampsia in the general population of Maryland is 1 in 490, or 20 per cent in contrast to a previous report of 1 per cent for pregnancies given hospitalization.

4. Eclampsia is five times as prevalent in the primigravidas as in multigravidas.

5. The negro population of Maryland showed an incidence of 1 in 310 or 32 per cent.

6. Eclampsia is two and one-half times more prevalent in multiple pregnancy.

7. Recurring eclampsia is severe and carries a high mortality.

8. Ante-partum eclampsia is the most severe type.

9. Forty-six per cent of the patients suffering from eclampsia before delivery were treated radically.

10. The total maternal mortality was 20.4 per cent.

11. Post-partum eclampsia in the multigravida is most fatal with a mortality of 32 per cent.

12. Cases handled conservatively had a mortality of 12 per cent in contrast to 34 per cent for those treated radically.

13. The total fetal mortality was 30.2 per cent and the risk for the baby is greater if mother receives conservative treatment.

14. The desired grade of prenatal care is outlined.

15. Fifty-four per cent of the patients receive no prenatal care. Very few receive adequate care.

16. Early detection and control of the preeclamptic is the means of attacking eclampsia.

17. Both incidence and mortality of eclampsia are diminished by adequate prenatal care.

The authors desire to thank the various hospitals for their cooperation in this study and the Baltimore City Health Department for the general statistics furnished.

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The treatment of choice in cases of acute mastitis is roentgen ray therapy, applied early and repeated at definite intervals. In this way operation may be avoided in almost 100 per cent of cases, recurrences are prevented and nursing is maintained.

J. P. GREENHILL.

ERYTHROBLASTOSIS

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ERYTHROBLASTOSIS of the newborn has been considered a rare disease. Isolated cases of hydrops fetalis, icterus gravis neonatorum, and congenital anemia appear frequently in the literature. This impression of rarity is contradicted, however, by Ballantyne[1] who was able to collect 70 cases of hydrops fetalis from the literature prior to 1892. In 1931, Ferguson[5] added a series of 7 cases with autopsies, including both icterus gravis neonatorum, and congenital hydrops. Similarly, Clifford and Hertig[2] presented a small series of cases. Diamond, Blackfan, and Baty[4] contributed a complete review of the literature prior to 1934, and a larger series of cases, including congenital hydrops, icterus gravis, and congenital anemia of the newborn. With the exception of the paper by Clifford and Hertig[2] there has been no attempt to determine the incidence of the disease in a large obstetric service, nor has the obstetric history of women, following the birth of an erythroblastotic child, been investigated. With these facts in mind an analysis of all cases of erythroblastosis occurring in the Boston Lying-in Hospital since 1931 has been made. In addition, the mothers have been interviewed personally in every case where they could be located, and their child-bearing histories analyzed.

In attempting such an analysis certain arbitrary criteria for the diagnosis and classification of erythroblastosis had to be established. All newborn infants showing edema, either generalized or peripheral, associated with a large liver and spleen, extramedullary erythropoiesis and an increase in the number of circulating nucleated red cells, were classified as having erythroblastosis of the hydrops type. The additional presence of jaundice or anemia did not change the classification of the case. However, an infant either born icteric or becoming so within the first forty-eight hours of life, and possessing an enlarged liver and spleen, and an increase in the circulating nucleated red cells, but at no time showing any edema, was classified as having erythroblastosis of the icterus type. The addition or development of severe anemia did not change the classification. There remained in the group, entitled "erythroblastosis of the anemic type," only those infants having severe congenital anemia, an enlarged liver and spleen, and an increase in nucleated red cells, but never showing either jaundice or edema. All infants showing the presence of infection or any congenital anomaly, either during life or at autopsy, were eliminated. No infants whose mothers had positive blood tests for syphilis* were included.

*The Hinton Test is used throughout, unless otherwise specified.

There was a small group of infants who showed no clinical signs of erythroblastosis but whose placentas, on examination, showed an increase in the nucleated red cells in the fetal circulation. These infants have not been included because it was felt that many conditions, i.e., partial asphyxia during birth, could cause a temporary rise in the nucleated red cells. An arbitrary level of 15 per cent, or greater, has been taken as an abnormal increase in nucleated red cells in the newborn. This is well in advance of the levels reported by Lippman,[6] Wintrobe and Shumacker[8] and others.

CASE REPORTS

Type: Congenital Hydrops

CASE 1.—Mrs. M. K. (2827.) The mother was a 37-year-old American born, para ii. Her first pregnancy, in 1930, terminated normally except that the child was born by breech mechanism. The child was living and well at the time of this pregnancy. The patient's past history was not essential. She was in excellent health during this pregnancy. The delivery occurred at term, on Nov. 1, 1931, and was normal in every respect. The child was a 2,880 gm. female who never breathed well. In spite of all efforts, the infant died three hours after birth. The mother had a negative blood test for syphilis at this time.

The placenta weighed 1,160 gm. The maternal surface was pale in color, deeply fissured in appearance, firm in consistency, but extremely friable. Microscopically, the syncytial cells were immature in appearance. The Langhans layer was partially retained. The stroma was both hyperplastic and edematous. There were many Hofbauer cells present. The vessels were reduced in number and were filled with nucleated red blood cells, those of the erythroblastic type predominating. There were areas of intracapillary erythropoiesis.*

At autopsy, the body was that of a well-developed white female with generalized edema, most marked on the right side. The skin had a slightly icteric tinge and showed many petechiae. There was slight pulmonary congestion and edema, and moderate ascites. The heart weighed 34 gm. (normal full-term weight, 17 gm.) and showed hypertrophy and dilatation of all chambers. The liver was twice normal size and the spleen was enlarged six times. Both organs showed marked erythropoiesis. In addition, there were erythropoietic foci in the adrenals, thymus, and kidneys. Both grossly and microscopically, the bone marrow was hyperplastic, with many primitive red cells in the trabecular spaces. The mother could not be located on the follow-up in January, 1937.

CASE 2.—Mrs. S. C. (RH 864.) The mother was a 36-year-old white American, para iv. She had had her first children normally in 1926 and 1929, respectively. The third child, delivered by Kerr cesarean section on Dec. 13, 1930, because of dilatation and curettage, perineorrhaphy, suspension, and repair of recti, following her second pregnancy, was jaundiced at birth and died in a few hours with a clinical diagnosis of icterus gravis neonatorum. This was confirmed at autopsy. Her past medical and family histories were noncontributory. Other than the previously mentioned operation, she had always been in good health. There was an interval of two years between the third and fourth pregnancy. Her prenatal course during this pregnancy was uneventful. She was subjected to a repeat classical cesarean section at term on March 10, 1932. The baby was a large, pallid male child with advanced generalized edema. It never breathed properly and died thirty-eight minutes after birth.

The placenta weighed 1,230 gm.

*The remaining placentas in the group are pathologically identical; therefore only the weights will be given.

At autopsy there was revealed the body of a well-developed white male infant with advanced generalized edema. There was moderate hydrothorax, hydropericardium, and ascites. The heart weighed 40 gm. and showed hypertrophy and dilatation of all chambers. The liver and spleen weighed 200 gm. and 50 gm., respectively. Microscopically, there were foci of erythropoiesis in the liver, spleen, lungs, pancreas, kidney, prostate, thyroid, and dura of the spinal cord.

On follow-up this patient had had no more children. A blood test for syphilis was not taken.

CASE 3.—Mrs. O. B. (RH 2420.) The mother was a 22-year-old white American born, para ii. The first child, born in 1929, was perfectly normal. The past medical, surgical, and family histories were non-contributory. Her antepartum course during this pregnancy was normal. The mother had a negative blood test for syphilis at this time. She was delivered normally at term, on June 23, 1932, of an edematous, 3,240 gm. male infant, covered with yellow vernix. The child died twenty-two minutes after delivery. The mother had an uneventful convalescence.

The placenta weighed 1,150 gm.

At autopsy the body was that of a well-developed, male child with advanced generalized edema. There were a slight hydrothorax and ascites. The heart weighed 26 gm. The liver and spleen weighed 170 gm. and 24 gm., respectively. Microscopically, there were foci of erythropoiesis in the liver, spleen, kidney, thymus, heart, mesentery, and aortic adventitia. There were petechiae in the brain and epicardium, and an old subcapsular hemorrhage in the spleen. There was an incidental small subarachnoid hemorrhage.

On follow-up, the patient had a subsequent normal child, born three weeks from term, in 1933. The child was living and well at the time of the follow-up examination in April, 1937. The patient had an incomplete abortion and dilatation and curettage in 1935. Her blood test for syphilis was still negative.

CASE 4.—Mrs. A. G. (786.) The mother was a 33-year-old colored para ix. Her first two pregnancies resulted in normal babies. The third and fourth pregnancies were terminated by miscarriages at six weeks. Her fifth and sixth pregnancies, in 1930 and 1931, respectively, resulted in normal children. Neither she nor her husband presented any significant family, medical, or surgical history. Her prenatal course during this pregnancy was entirely normal. Her blood test for syphilis was negative. She was delivered, at term, on Aug. 16, 1932, of a stillborn footling, breech, with a prolapsed cord. The child was an edematous female weighing 2,910 gm.

The placenta weighed 1,140 gm.

At autopsy, the body was that of a well-developed, colored female, showing advanced generalized edema, and many petechiae in the skin. There was moderate ascites and hydropericardium. The heart weighed 25 gm. and showed hypertrophy and dilatation of all chambers. The liver and spleen weighed 109 gm. and 25 gm., respectively. There was, in addition, a tentorial tear with massive intracranial hemorrhage. Microscopically, foci of erythropoiesis were found in the liver, spleen, thymus, retroperitoneal lymph nodes, adrenals, kidneys, and pancreas.

The patient was seen again in February, 1937. She had had an ectopic pregnancy with removal of a tube and ovary in 1934. Then, in 1935, she had a perfectly normal child which was living and well at the time of the follow-up visit. A blood test, taken during this visit, was positive (Hinton test). A check-up showed the Wassermann to be positive also.

CASE 5.—Mrs. E. R. (RH 2616.) The mother was a 32-year-old American, para iv. Her first child, born in 1920, was entirely normal. Following this delivery, she had inversion and perforation of the uterus. This was repaired and she had a moderately stormy convalescence. The second child born in 1930, died at three days of age with jaundice, hepatomegaly, splenomegaly, and foci of erythropoiesis in the liver and spleen. The third child was born at home in 1931. The infant was severely jaundiced at birth, but the mother refused to allow it to be transferred to a hospital. In spite of intense jaundice of long duration, the child did well and was in good health at the time of this pregnancy. The mother's family his-

tory was noncontributory except for the fact that her younger brother was born jaundiced. Her past history was noncontributory. She had a slight amount of albumin and slight hypertension during the prenatal period of this pregnancy. Her blood test for syphilis was negative. She went into labor spontaneously six weeks before her expected date of confinement, on Oct. 28, 1932. She was delivered of a stillborn female footling, breech, weighing 3,840 gm. The child had advanced generalized edema. The mother's convalescence was normal.

The placenta weighed 1,040 gm.

At autopsy, the body was that of a well-developed, white, female infant with advanced generalized edema. There were numerous petechiae in the skin. The viscera had a slightly icteric tint. There were numerous subserosal petechiae. A slight ascites was present. The heart was normal in weight. The liver and spleen weighed 156 gm. and 39 gm., respectively. Microscopically, there were foci of erythropoiesis in the liver, spleen, kidney, duodenum, adrenal, thymus, and lymph nodes.

On follow-up in April, 1937, the mother and children were well. She had had an induced abortion in 1933 and then no further pregnancies. The blood test for syphilis was still negative.

CASE 6.—Mrs. R. C. (5279.) The mother was a 40-year-old, white, para xi, whose first child, born in 1915, died within twenty-four hours after birth of an unknown cause. The second and fourth children, born in 1921 and 1922, respectively, died of pneumonia during the first year. The ninth child, born in 1929, a month premature, died at birth. All the other children had normal births and were living and well at the time of this pregnancy. The patient's past history and family history were noncontributory. Her course during this pregnancy was uneventful. She had a negative blood test for syphilis. She gave birth to a 2,490 gm. stillborn, edematous, female child, the fetal heart having stopped two or three days before birth. The mother's convalescence was uneventful.

The placenta weighed 800 gm.

At autopsy, the body was that of a small female child showing some maceration and advanced generalized edema. There was a large amount of straw-colored fluid in the abdominal cavity. The liver and spleen weighed 121 gm. and 20 gm., respectively. There was slight hypertrophy and dilatation of the heart. It weighed 24 gm. There were petechiae in all the abdominal viscera. Microscopically, there was some maceration in all the organs. There were foci of erythropoiesis in the liver, spleen, kidneys, and thymus. The bone marrow showed considerable erythropoietic activity.

On follow-up, in February, 1937, the patient had died with a questionable diagnosis of tuberculosis two years after the birth of this child. She had had no other pregnancies.

CASE 7.—Mrs. E. M. (2832.) The mother was a 30-year-old, white, American born, para iv. The first three children were born in 1927, 1928, and 1930, respectively. At the time of this pregnancy they were all living and well. Her medical, surgical, and family histories were noncontributory. Her prenatal course during this pregnancy was uneventful. She went into labor spontaneously, at term, on Oct. 4, 1932, and was delivered by low forceps of an edematous, 3,890 gm., white, female infant. The child was covered with golden yellow vernix, and lived only two and one-half hours. The mother's postpartum course was uneventful.

The placenta weighed 1,220 gm.

At autopsy, the body was that of a well-developed, white, female child, showing advanced generalized edema. Both ascites and hydrothorax were present. The liver and spleen weighed approximately 234 gm. and 40 gm., respectively. The heart was twice its normal size. Microscopically there were foci of erythropoiesis in the liver, spleen, kidney, and serosa of the small intestine.

On the follow-up, in February, 1937, the patient was well. She had had a normal pregnancy in 1935 and the child was living and well. Her blood test for syphilis was still negative.

CASE 8.—Mrs. M. D. (RH 2777.) The mother was a 25-year-old, white, American born, para ii, whose first child was born in 1933. This child was living and well at the time of this present pregnancy. The mother's past and family histories were noncontributory. The prenatal course during this pregnancy was entirely uneventful. She was delivered normally, at term, on Jan. 27, 1934. The child was a 3,420 gm. male infant covered with yellow vernix and having generalized pitting edema. It was in very poor condition, and in spite of a small transfusion became jaundiced and died eleven hours after birth. The mother's convalescence was uneventful.

The placenta weighed 865 gm.

At autopsy, the body was that of a well-developed, male infant with advanced pitting edema and generalized icterus. There was a slight right hydrothorax and hydropericardium. The heart was enlarged, weighing 32 gm. It showed hypertrophy and dilatation of all chambers. The liver and spleen weighed 193 gm. and 30 gm., respectively. Microscopically there were foci of erythropoiesis in the liver, spleen, and kidneys. There was an incidental left subdural hemorrhage.

On follow-up, in April, 1937, the patient had had an induced abortion in 1935. There had been no further pregnancies. The blood test for syphilis was negative.

CASE 9.—Mrs. E. C. (12938.) The mother was a 37-year-old, white, American born, para iv, whose first three children were living and well at the time of this pregnancy. Her past and family histories were noncontributory. She had an entirely negative prenatal course during this pregnancy. Because of a partial placenta previa, and acute hydramnios, the membranes were ruptured at the eighth month of gestation. There was breech presentation and a foot was easily brought down. The child was stillborn and macerated. It weighed 2,730 gm. The mother's postpartum course was uneventful.

The placenta weighed 990 gm.

At autopsy the body was that of a macerated edematous female fetus, measuring 46 cm. in length. The body cavities all contained free bloody fluid. The heart weighed 23 gm. and showed slight hypertrophy. The liver and spleen weighed 158 gm. and 25 gm., respectively. Unfortunately the tissues were too macerated for microscopic study.

On follow-up, in February, 1937, the patient was well. She had had no further pregnancies. She refused to submit to a blood test.

CASE 10.—Mrs. E. C. (13267.) The patient was a 37-year-old, white, American born, para vii. Her first four children were delivered normally in 1923, 1924, 1927, and 1932, respectively, and were living and well at this pregnancy. The fifth baby, born in 1932, was stillborn, at another hospital. The cause of death was unknown. Medically, her past and family histories were not essential. The sixth child weighed 3,960 gm., and was delivered stillborn in 1934, after a prenatal period complicated by mild toxemia and hydramnios.

The placenta weighed 1,350 gm.

There was no autopsy. The mother's puerperium was uneventful.

The seventh child was born one year later. The prenatal period during this pregnancy was uneventful except for a short fetal systolic murmur heard during the last weeks of pregnancy. The patient was admitted two weeks from term, on Dec. 6, 1935, in labor. She was delivered normally of a large edematous male infant which lived thirty minutes. It was covered with yellow vernix.

The placenta weighed 1,275 gm.

At autopsy, the body was that of a well-developed, white, male infant measuring 50 cm. in length. There was soft pitting edema round the neck, of the extremities, and of the genitalia. The skin was slightly icteric, and there were a few ecchymotic areas. There was moderate ascites. The heart weighed (estimated) 40 gm. and showed hypertrophy and dilatation of all chambers. Both splenomegaly and hepatomegaly were present, these organs weighing 120 and 190 gm., respectively. There were petechiae in the skin, thymus, and renal cortex. Microscopically, there was erythropoiesis of the liver, pancreas, kidneys, and adrenals.

On follow-up in February, 1937, the mother had had no more pregnancies. The blood test for syphilis was still negative.

CASE 11.—Mrs. F. K. (20651.) The patient was a 27-year-old, white, American born, para iii, who had had two normal pregnancies, one in 1931, and the second in 1934.

She had had a 12-pound tumor removed from the left kidney when she was one month pregnant. Medical and surgical histories were otherwise negative. Six weeks prior to delivery, the patient noticed numbness of the right leg, lasting two weeks. For two weeks prior to delivery she had marked edema of the ankles, legs, and face. She felt fetal movements until ten days prior to admission at which time they stopped. On admission, her blood pressure was 164/102, and she showed a trace of albumin in the urine. The blood test for syphilis was negative. Because of presumable fetal death and rapidly developing toxemia, the membranes were ruptured on Oct. 21, 1936, eight weeks from term. Seven hours later she went into labor and delivered a macerated edematous still-born fetus, weighing 2,355 gm. She had a slight febrile puerperium complicated by a hemorrhagic retinitis.

The placenta weighed 1,790 gm. It showed the characteristic pathologic changes.

An autopsy permission was not obtained.

On follow-up, six months later, the mother was well. The blood test for syphilis was negative.

CASE 12.—Mrs. H. B. (71756.) The mother was a 29-year-old, white, American born, para v. She had had two miscarriages and two normal living children. The fourth child was stillborn. Her family and past histories were noncontributory. Her prenatal course during this pregnancy was normal until two weeks prior to admission when she began to have headaches. She developed a rapidly progressive type of preeclampsia and was admitted as an emergency with edema of the hands, face, and extremities, a blood pressure of 150/90, and a large trace of albumin in the urine. In spite of therapy she became progressively worse. On March 24, 1937, when she was eight weeks from term, a Braxton Hicks version was done and a foot brought down. She was then allowed to go into labor and after thirteen and one-half hours she delivered a stillborn 2,880 gm. female infant with generalized edema. The placenta failed to separate and it was necessary to resort to manual extraction. This was followed by so severe a hemorrhage that a 400 c.c. transfusion was necessary. The patient improved rapidly and was discharged on the seventeenth day. The laboratory test of the blood was negative for syphilis.

The placenta weighed 1,260 gm.

At autopsy, the body was that of a well-developed, female infant with advanced generalized edema. There was no jaundice. There was an advanced hydrothorax and ascites. The heart weighed 8 gm. and showed hypertrophy and dilatation, considering the degree of prematurity. The liver and spleen weighed 90 gm. and 10 gm., respectively. On section there were foci of erythropoiesis in the liver and spleen.

On follow-up, six weeks post partum, the patient was well.

CASE 13.—Mrs. H. W. (14577.) The mother was an American born, white, 39-year-old, para xii. She had had eight previous normal pregnancies in 1914, 1916, 1917, 1918, 1920, 1921, 1925, and 1927. One of twins, born in 1921, died at birth. The ninth child, born in 1929, was stillborn and weighed over 15 pounds. It was said to have had the cord around the neck. The tenth child, stillborn in 1932, according to the mother was both jaundiced and edematous. Her past and family histories were noncontributory. Her prenatal course during the eleventh pregnancy was normal except for the fact that she was markedly overweight. Her weight was 175 pounds. The blood test for syphilis was negative. She was delivered normally, at term, of a nine-pound male infant on Sept. 12, 1934. The child was both edematous and icteric at birth. In spite of transfusions, it lived only forty-eight hours.

Unfortunately, the placenta was not saved.

At autopsy, the body was that of a well-developed and well-nourished male infant with advanced icterus and peripheral pitting edema. There was no increased fluid in the body cavities. The heart weighed 36 gm. and showed hypertrophy and dilatation of all chambers. The liver weighed 414 gm. The spleen was also enlarged, weighing 63 gm. The kidneys, too, were increased in size, weighing 22 gm. each (normal, right 14, left 14 gm.). There was kernicterus of the brain. Microscopically, there was erythropoiesis of the spleen, liver, kidneys, and adrenals. Petechiae were present in the epicardium, kidney, adrenal, lungs, and bladder.

The twelfth pregnancy occurred in 1937. She entered the hospital on April 6, 1937, seven weeks from term. She had gained 20 pounds in weight and had had dyspnea and orthopnea for six weeks. The blood pressure was 154/92. She showed a slight trace of albumin. In spite of all therapy and restricted diet, the patient failed to improve. The laboratory test for syphilis in the blood was negative. She went into labor spontaneously on April 12, 1937. During labor she began to bleed profusely. A foot was immediately brought down and a Spanish windlass applied to the mother's abdomen. Two transfusions were given. When the cervix was nearly fully dilated a breech extraction was done and a stillborn, edematous, female infant weighing 3,600 gm. was delivered. The mother did well during her postpartum period except for a day or two of partial anuria immediately following delivery.

The placenta weighed 1,300 gm.

At autopsy, the body was that of a well-developed female, measuring 47 cm. in length. There was generalized edema, most marked over the head, neck, and body. There were many petechiae in the skin over the thorax. There was no jaundice. The abdomen contained approximately 300 c.c. of brownish-yellow clear fluid. The heart showed hypertrophy and dilatation of all chambers. It weighed 30 gm. The liver and spleen weighed 300 gm. and 88 gm., respectively. The bone marrow was hyperplastic. On microscopic section there were foci of erythropoiesis in the liver, spleen, kidney, pancreas, adrenals, and submucosa of the intestine.

Type: Icterus Gravis

CASE 1.—Mrs. S. C. (RH 864.) For case history, see same mother in the preceding group of cases.

The placenta was not saved for examination.

At autopsy, the body was that of a well-developed white female, measuring 54.5 cm. in length, and weighing 3,300 gm. The skin was moderately icteric. There was no edema. There was no excess fluid in any of the body cavities. The heart was normal in size. The liver was not weighed, but was said to be normal in size. The spleen weighed 24 gm. There were petechiae in the brain and viscera. Microscopically the liver, spleen, and kidneys showed many foci of erythropoiesis.

CASE 2.—Mrs. M. O'D. (7302.) The mother was a 32-year-old, white, American born, para iv, whose first child was born in 1919. She had had twins in 1920. These three children were living at the time of this pregnancy. The third pregnancy, terminating in 1922, resulted in an extremely jaundiced infant who died at four days of age. The family history was noncontributory. She had a cholecystectomy in 1930. Her prenatal course during this pregnancy was uneventful. Her blood test for syphilis was negative. She was delivered normally at term after seventeen hours of labor, on Feb. 23, 1931. The child was a normal female weighing 4,230 gm. It became jaundiced within the first day of life. The liver and spleen were enlarged to palpation. The red count was 5.9 million. There were 69,000 nucleated cells, 44 per cent of which were red cells. The icteric index was 300. The child was given a transfusion of 50 c.c. of citrated blood. Two days later the physical findings were unchanged. The red count was 5.9 million. The next day the red count still remained high and there were no nucleated red cells.

The child continued to do well until nine days later, the mother left the hospital against advice, and took the baby with her. The mother had a normal post-partum course except for a thrombophlebitis of the left leg.

On follow-up in April, 1937, the mother and child were well. There had been no further pregnancies.

CASE 3.—Mrs. M. A. (5486.) The mother was a 26-year-old, American born, para iii. Her first two children were born in 1926 and 1929, respectively. Both were living and well at the time of this pregnancy. Her family and past histories were noncontributory. She had an entirely normal prenatal period during this pregnancy. The blood test for syphilis was negative. She went into labor spontaneously on Aug. 19, 1931, and was delivered normally of a 3,570 gm. female infant. The child appeared well but became progressively more jaundiced during the first two days of life. It died suddenly of respiratory failure on the third day after birth. Unfortunately the disease was not recognized clinically and no adequate blood studies were done. The mother's postpartum course was uneventful.

The placenta was not saved for examination.

At autopsy the body was that of a well-developed, white female infant, measuring 35 cm. from vertex to buttocks. There was a deep generalized icterus of the skin but no edema. There was slight hypertrophy and dilatation of the heart. It weighed 25 gm. The other organs were not enlarged. There were petechiae in the epicardium, endocardium, and esophageal mucosa. There was kernicterus of the basal ganglia of the brain. Microscopically, there were foci of erythropoiesis in the liver, spleen, lymph nodes, and adrenals.

On follow-up, in February, 1937, the mother was well. She had had no further pregnancies. She refused to have a blood test for syphilis.

CASE 4.—Mrs. M. G. (RH 1795.) The mother was a 33-year-old, white, American born, para vi, whose first child, born in 1922, was jaundiced at birth and died on the sixth day. The second child, born in 1924, was normal except for a birth palsy. The next three children, born in 1926, 1928, and 1930, respectively, were all deeply jaundiced at birth and died shortly thereafter. She had had an entirely normal prenatal course during all of her pregnancies. Her past and family histories were noncontributory. During this pregnancy she had a large irregular fibroid at the right cornua of the uterus. The prenatal course was uneventful. The blood test for syphilis was negative. She was given a diet, high in nucleoproteins, and rich in liver. She went into labor spontaneously at term, and Nov. 23, 1931, was delivered of a healthy, normal appearing child (male), weighing 3,840 gm. One hour after birth it was noted that there were ecchymoses on the right forearm. The child was immediately transfused with 90 c.c. of maternal blood. The next day the child was jaundiced. The following day the jaundice increased and sixty-five hours after birth the child suddenly became cyanotic and died. The spinal fluid was xanthrochromic.

Unfortunately the placenta was not saved for examination.

At autopsy the body was that of a well-developed male infant, measuring 47 cm. in length. There was advanced icterus of the skin and many small subcutaneous hemorrhages. There was no edema and no increase in fluid in the body cavities. The heart was not enlarged. The liver weighed 180 gm. The spleen weighed 28 gm. There was an area of acute infarction of the spleen. There were gross hemorrhages into the adrenal cortex, pleura, pituitary, and epicardium. There was a slight hyperplasia of the bone marrow. Microscopically there were multiple foci of erythropoiesis in the liver, spleen, adrenals, and pituitary. The bone marrow showed advanced erythroblastic activity.

On follow-up, in April, 1937, it was found that the patient had had a hysterectomy in November, 1932. There had been no intervening pregnancies. A blood test for syphilis was not done.

CASE 5.—Mrs. H. J. (6457.) The mother was a 38-year-old, para vi. She had had five children born in 1918, 1922, 1924, and 1928, respectively. The child born in 1922 died at the age of three months of convulsions. All the others were normal.

The mother's past and family histories were noncontributory. Her prenatal course during the pregnancy was entirely normal. The blood test for syphilis was negative. She entered the hospital two weeks overdue on Jan. 1, 1932, and was delivered normally on the same day of a female child. It was covered with golden yellow vernix. The child never breathed well. It was deeply cyanosed and during the first day both the liver and spleen were felt to be enlarged. The child appeared slightly better the next day, but it was slightly jaundiced. The jaundice deepened on the third day and the temperature rose to 102.6° F. The blood studies showed hemoglobin 96 per cent, red blood cells 3.94 million, white blood cells 34,153. There were 117,500 nucleated red cells and of these 68 per cent were normoblasts, 28 per cent erythroblasts, and 40 per cent myeloblasts. The bleeding time was fifteen minutes. The coagulation time was two to three minutes. A small transfusion was given. In spite of this, the course was progressively downhill. Another transfusion of 40 c.c. was given on the fourth day. Death occurred shortly after this. The mother's post-partum course was uneventful.

The placenta was not saved for examination.

At autopsy the body was that of a well-developed, well-nourished, white female, measuring 44.5 cm. in height. The skin and viscera were deeply jaundiced. There was no edema. The heart was slightly enlarged, weighing 23 gm. There was an early terminal bilateral bronchopneumonia with fibrinous pleurisy. The liver and spleen weighed 220 gm. and 25 gm., respectively. Grossly the bone marrow was hyperplastic. There were petechiae in the pleura, thymus, epicardium, pituitary, brain, kidneys, endometrium, and adrenals. Microscopic examination showed foci of erythropoiesis in the liver, spleen, adrenals, pancreas, and pituitary. The liver showed bile stasis. The bone marrow showed advanced hematopoietic activity with foci of erythroblasts and normoblasts.

On follow-up visit in February, 1937, the mother was living and well. She had had no further pregnancies. She refused to have a blood test for syphilis.

CASE 6.—Mrs. F. P. (9602.) The mother was a 28-year-old, white, American born, para vi. Her first four children, born in 1911, 1913, 1919, and 1923, were living and well at the time of this pregnancy. In 1930 she had an eight-month stillborn child. Between 1923 and 1930 she had married for a second time. Her family and past histories were negative. She had a normal prenatal course during this pregnancy. The blood test for syphilis was negative. She was delivered normally of a 4,230 gm. male infant on Dec. 7, 1932. The child appeared normal but became deeply jaundiced on the day after birth. Both the liver and spleen were enlarged. Blood studies showed 1.9 million red cells, 38,900 nucleated cells, of which 55 per cent were red cells. The patient was transfused immediately and during the next two weeks received 9 transfusions. The red count never rose above 2 million until the last transfusion. The nucleated red cells fell to 10 per cent during the first week. During this time, however, the jaundice deepened and reached an icteric index of 400. At the end of two weeks, nucleated red cells disappeared. The jaundice became less and the red count improved. The child was discharged six weeks after birth. The mother's post-partum course was normal.

The placenta was not saved for examination.

On follow-up in May, 1937, the mother and child were well. There had been no further pregnancies. The blood test for syphilis was refused.

CASE 7.—Mrs. S. L. (RH 2673.) The mother was a white, 38-year-old, American born, para ii. Her first child was normal. Her family and past histories were noncontributory. Her prenatal course during this pregnancy was entirely normal. The laboratory test for syphilis was not done. She was delivered normally of a 3,360 gm. male infant on Dec. 10, 1932. The child was covered with yellow vernix and quite cyanotic at birth. It never breathed well. Petechiae developed over the scalp. The liver and spleen were enlarged to palpation. Examination of the blood showed 4.1 million red cells, 14,000 nucleated cells, 64 per cent of which were red cells. The hemoglobin was 105 per cent. Clotting time was thirty minutes. Bleed-

ing time normal. In spite of a transfusion of 30 c.c. the child continued to do poorly. The nucleated red cells rose to 80 per cent of the nucleated cells. Jaundice appeared on the second day and the child died shortly thereafter. The mother had an uneventful convalescence.

Autopsy permission was not obtained.

The placenta weighed 570 gm.* It was of normal color and consistency, but the membranes were stained yellow. On section, the villi were slightly larger than normal. The syncytium was slightly immature. The stroma showed slight hyperplasia and edema. The vessels contained many nucleated red cells.

The mother developed mild diabetes during the next pregnancy in 1935. However, under adequate therapy she was delivered of a perfectly normal male infant.

On follow-up in May, 1937, there had been no further pregnancies. The blood test for syphilis was negative.

CASE 8.—Mrs. M. O'B. (10478.) The mother was a 39-year-old, white, American born, para vi. She had five previous normal children, born in 1917, 1921, 1922, 1924, and 1925, respectively. Her family history was noncontributory. Her father died of heart disease. She had had diphtheria at three years of age. Her prenatal course during this pregnancy was normal. She was delivered, at term, on April 8, 1933, of a 4,350 gm. male infant. The child became slightly jaundiced within fourteen hours. The jaundice did not increase, but on April 18, the child became listless and pale and for the first time the spleen became palpable. Blood studies showed hemoglobin 50 per cent, red blood cells 2.5 million, nucleated red cells 10 per cent of the nucleated cells. The child was given a transfusion of 50 c.c. of citrated blood. The red count rose to 3.07 million, and the child was discharged well on April 24, 1933. The mother's post-partum course was uneventful.

The placenta was not saved for examination.

On follow-up in April, 1937, the mother and child were living and well. She had a normal child born in 1935 and following this there were no other pregnancies. The blood test for syphilis was negative.

CASE 9.—Mrs. C. S. (11649.) The mother was a 27-year-old, white, American born, para ii. The first child was delivered by high forceps in 1931. It was living and well at the time of this pregnancy. The mother's past and family histories were noncontributory. Her antenatal course during this pregnancy was uneventful. Her blood test for syphilis was negative. She was delivered at term on Aug. 17, 1933, of a 3,880 gm. male infant. The child appeared normal and cried lustily. However, it was covered with a golden yellow vernix. About eight hours after birth the child developed a deep jaundice and pallor. The liver and spleen were greatly enlarged. Blood studies showed only 1.82 million red cells, 7,800 nucleated cells, 33 per cent of which were red cells. X-ray on the third day showed considerable cardiac enlargement. The child received a total of 18 transfusions at one- to four-day intervals. The nucleated red cells dropped to 11 per cent of the nucleated blood cells within ten days and remained at that level. After five weeks he was transferred to the Children's Hospital. At the time of transfer the red count was only 2 million. He was discharged from there ten weeks after birth with the anemia little alleviated. The mother's post-partum course was uneventful.

The placenta weighed 690 gm.

On follow-up in January, 1937, the mother and both children were well. The mother had had a twenty weeks' miscarriage and no other pregnancies. The blood test for syphilis was still negative.

CASE 10.—Mrs. A. MacD. (15339.) The mother was a 37-year-old, white, American born, para iv, with two living children born in 1927 and 1930, respectively. All her deliveries were by cesarean section, the reasons for which were obscure. In 1933 she had another section, at which time the child was stillborn. The family history was negative. The patient had an appendectomy in 1922. Otherwise her

*The placentas in this group show similar pathologic changes and so only the weights will be given.

past history was not unusual. Her prenatal course during this pregnancy was not remarkable, except for the fact that she showed a slight trace of albumin just before entering the hospital. The blood test for syphilis was negative. A repeated classical cesarean section was done three weeks before term, on Dec. 22, 1934. At this time the mother was sterilized by the Irving technique. The child weighed 3,315 gm. and was to all appearances normal. However, it became jaundiced three hours after birth. The liver and spleen were clinically enlarged, and blood studies showed the hemoglobin to be 100 per cent, red blood cells 4.8 million, nucleated cells 62,000, with 80 to 85 per cent of these red blood cells. Most of the nucleated red cells were erythroblasts. A transfusion of 45 c.c. was immediately given. The following day the jaundice increased rapidly and the red count dropped to 2.8 million. The child developed a severe epistaxis, on the third day, and this could not be stopped. In spite of another transfusion, death occurred thirty hours after birth. The mother's convalescence was uneventful.

At autopsy the body was that of a well-developed, white, male infant, measuring 50 cm. in length. The skin and scleras were diffusely icteric, having a peculiar orange-yellow color. The peritoneal cavity contained a small amount of dark fluid. There was no increase of fluid in any of the other body cavities. The heart weighed 26 gm. and showed slight hypertrophy and dilatation of all chambers. The liver and spleen weighed 174 gm. and 44 gm., respectively. Grossly, the brain showed kernicterus of the basal nuclei. There were petechiae in the lungs, spleen, pericardium, bladder, and pleura. The bone marrow was not hyperplastic. Microscopically there were multiple foci of erythropoiesis in the liver, spleen, kidney, and pancreas. There was slight hyperplasia of the bone marrow with islands of erythroblasts.

The placenta was not saved for examination.

On follow-up examination in March, 1937, the mother was well. There had been no further pregnancies. The blood test for syphilis was not done.

CASE 11.—Mrs. N. H. (13929.) The mother was a 32-year-old, white, American born, para iii. Her first two children were normal in every respect. Her family and past histories were noncontributory. Her prenatal course during this pregnancy was normal. The blood test for syphilis was negative. She was delivered normally, at term, on March 14, 1937, of a 3,090 gm. jaundiced male infant. Both the liver and spleen were slightly enlarged. Blood studies showed 6 million red cells, 48,000 nucleated cells of which 26 per cent were red cells. The following day the red count fell to 5.1 million and the nucleated cells were 36,700. Ninety-seven per cent of these were red cells. The child was given transfusions on the second, third, and fifth days. The red count remained at 4 million until the eighth day when it fell to 1.5 million. The child was again transfused on the eighth and tenth days. The red count then remained above 4 million. The nucleated red cells disappeared from the blood stream on the fifteenth day. The jaundice gradually disappeared during the third week. The child was discharged five weeks after birth. However, it never developed normally and has had to remain in an institution. The mother's convalescence was normal.

The placenta was normal grossly. It was not saved for microscopic examination.

When seen in April, 1937, the mother was again pregnant. The blood test for syphilis was still negative.

CASE 12.—Mrs. D. B. (16449.) The mother was a white, 39-year-old, American born, para v. Her children, born in 1924, 1926, 1929, and 1931, were all living and well at the time of this pregnancy. The mother's family history was noncontributory. She had had her tonsils and adenoids removed in childhood. She stated that she had had an embolism following the birth of her fourth child. She had a very slight degree of hypertension during the last part of this prenatal period. Her blood test was negative for syphilis and otherwise her course during this pregnancy was normal. She was delivered normally at term, on April 5, 1935, of a male infant

weighing 3,360 gm. The child appeared normal, but developed jaundice during the second day. The liver and spleen were palpable at this time and blood studies showed 2.5 million red cells, 8,500 nucleated cells, with 50 per cent of these being red cells. The child was immediately transfused. The next day the nucleated red blood cells dropped to 35 per cent of the nucleated cells. Six days later the red cell count was 2.5 million. The child was again transfused and the red count rose to 2.5 million and remained there until discharge twenty days after birth. The mother's convalescence was uneventful.

The placenta weighed 650 gm.

On follow-up in March, 1937, her children were all living and well. The mother had had no further pregnancies and the blood test for syphilis was still negative.

CASE 13.—Mrs. G. F. (16827.) The mother was a 28-year-old, American born, white, para iii whose first child, born in 1932, was living and well at the time of this pregnancy. The second child, born in 1933, one month prematurely, was said by the father to have died of jaundice at three weeks of age. The mother's family and past histories were noncontributory. Her prenatal course was perfectly uneventful except for a slight elevation in blood pressure and slight albuminuria. Her blood test for syphilis was negative. She was delivered normally, at term, on May 19, 1935, of a 3,210 gm. female infant. The child became jaundiced shortly after birth. The liver and spleen were both palpable and moderately enlarged. Blood studies showed 2.21 million red cells and 63,000 nucleated cells, 64 per cent of which were red cells. The child was given an immediate transfusion with 65 c.c. of citrated blood. The next day the red count was 3.4 million. There were 82,000 nucleated cells, 58 per cent of which were red cells. There was rapid improvement and the patient was discharged well on the fourteenth day. The mother's postpartum course was uneventful.

The placenta weighed 460 gm.

On follow-up in April, 1937, the mother and child were well. There had been no further pregnancies. The blood test for syphilis was still negative.

CASE 14.—Mrs. J. R. (5113.) The mother was a 43-year-old, Irish born, para v. Her children were born in 1918, 1921, and 1930, respectively. They were normal. The fourth child, born in 1931, died of an intracranial hemorrhage. Her family history was noncontributory. She had been a known diabetic for two years preceding this pregnancy. Her blood test for syphilis was negative. However, subsequent examination showed the husband to have a positive blood test for syphilis. She gave birth to a jaundiced 5,130 gm. female infant on Aug. 1, 1935. The child's face was covered with petechiae. The spleen and liver were both enlarged. The blood studies showed 4.3 million red cells, 55,000 nucleated cells, 80 per cent of which were red cells. She was given a transfusion of 45 c.c. of citrated blood. The next day the child showed typical signs of intracranial hemorrhage. Four days later she became severely jaundiced. The red count dropped to 3.2 million. The nucleated cells numbered only 9,000 and the red cells included only 14 per cent. The liver and spleen were noticeably increased in size. Because of a severe anemia she was transfused on the eleventh day and parental fluids were given at intervals. She was transfused again on the thirteenth, fifteenth, seventeenth, twenty-fifth, and thirty-fourth days. After this the blood tended to remain around 3.5 million. The jaundice had disappeared with the onset of the anemia on about the thirteenth day. The child's blood test for syphilis was negative. The child was discharged on the fifty-third day. The mother's post-partum course was uneventful, except for a few insulin reactions.

The placenta was not saved for examination.

On follow-up in April, 1937, the patient had had no further pregnancies. The condition of both mother and baby was good.

CASE 15.—Mrs. A. F. (8844.) The mother was a 23-year-old, white, American born, para iii. Her first child, born in 1932, was living and well at the time of this pregnancy. Her second pregnancy resulted in a stillborn infant. Her family history was negative. She had had whooping cough, and a tonsillectomy and

adenoidectomy in childhood. Her prenatal course during this pregnancy was normal. Her blood test for syphilis was negative. She was delivered by low forceps, at term, on December 5, 1935. The child, a male, weighed 3,750 gm. and was jaundiced at birth. On physical examination, the liver and spleen were enlarged and blood studies showed 2.8 million red cells and 31,000 nucleated cells of which 76 per cent were red cells. The child was immediately given a transfusion of 80 c.c. of citrated blood. The red count rose to 3.8 million. He was transfused again on the third, seventh, eleventh, thirteenth, and forty-third hospital days. On discharge, the red count was 3.8 million and none of the red cells were nucleated. The mother's post-partum course was normal. The placenta weighed 735 gm.

On follow-up in February, 1937, the child and mother were well. She had had no further pregnancies and her blood test for syphilis was still negative.

CASE 16.—Mrs. G. B. (19067.) The patient was a 21-year-old, white, American born, para ii. She had one previous child, born in 1933, who was living and well at the time of this pregnancy. Her family history was noncontributory. She had had purpura hemorrhagica during childhood. In 1922 she had a tonsillectomy and adenoidectomy. In other respects her past history was not essential. Her antenatal course during this pregnancy was entirely normal. Her blood test for syphilis was negative. She was delivered at term on Jan. 31, 1936, in the out-patient department. The child, a male, weighed 3,720 gm., and was apparently in good health. It developed jaundice during the first twelve hours. This became progressively worse during the next five days. A smear was reported negative for erythroblasts by the externe. The child died suddenly on the sixth day. The mother's post-partum course was uneventful.

The placenta was not saved for examination.

At autopsy, the body was that of a well-developed male infant, measuring 50 cm. in length. There was a deep icterus of the skin and viscera. There was no edema and no increase of fluid in the body cavities. The heart weighed 21 gm. The liver and spleen weighed 134 gm. and 30 gm., respectively. There was kernicterus of the basal nuclei of the brain. On microscopic examination there were many foci of erythropoiesis in the liver, spleen, and pancreas. The vertebral bone marrow showed advanced erythroblastic activity.

The follow-up examination in March, 1937, showed the mother to be pregnant again. The blood test for syphilis was still negative.

CASE 17.—Mrs. N. J. (19742.) The mother was a 30-year-old, white, Irish born, para iv. Her three previous children were born in 1932, 1933, and 1934, respectively. The first two were normal. The third was born jaundiced and did poorly during its early life. They were all living and well at the present pregnancy. Her family history was noncontributory. She had a vaginal repair and appendectomy in 1936. Her prenatal course during this pregnancy was uneventful. Her blood test for syphilis was negative. She was delivered normally, at term, on July 1, 1936, of a 2,865 gm. male infant. The child was in good condition but pale in color and slightly jaundiced. The liver and spleen were not felt. Blood studies showed the hemoglobin to be 64 per cent, red blood cells 2.4 million, nucleated cells 35,600, of these 26 per cent were red cells. The child was immediately transfused with 50 c.c. of the mother's blood. The next day the liver and spleen were palpable but the red cell count had risen to over 5 million. Three days later the jaundice had disappeared. The liver and spleen were not palpable and the nucleated red cell count had dropped to 10 per cent of the nucleated cells. A week later the red count dropped to 3.07 million and the child received a 45 c.c. transfusion. It was discharged two days later. The mother's puerperium was uneventful.

The placenta was not saved for examination.

On follow-up in April, 1937, the mother and baby were well. She had had a ten-weeks miscarriage in March, 1937. The blood test for syphilis was still negative.

CASE 18.—Mrs. D. C. (69750.) The mother was a 28-year-old, American born, white, para iv. Her first two children, born in 1926 and 1931, respectively, were

living and well at the time of this pregnancy. The third child, born in 1932, died of "jaundice" at four days of age. The family and past histories were noncontributory. She had a normal prenatal course during this pregnancy. The blood test for syphilis was negative. She was delivered, at term, on Sept. 17, 1936, of a 3,660 gm. male infant. The child became jaundiced soon after birth. The jaundice deepened, but it was not until the child became very pale and apathetic on the eighth day, that any alarm was felt. Blood studies then showed 1.86 million red cells. There were only two nucleated red cells per 100 nucleated cells. The child was given a 75 c.c. transfusion. The red cells promptly rose to 4.98 million. Two days later the red count had again fallen to 2.9 million and the nucleated red cells made up 10 per cent of the nucleated cells. Another transfusion was given and the red count rose to over 4 million where it remained in spite of a mild omphalitis occurring during the third week. The child was discharged five weeks after birth. The mother's post-partum course was normal. The placenta was not saved.

On follow-up in April, 1937, the mother and baby were living and well. There have been no further pregnancies. The blood test for syphilis was negative.

CASE 19.—Mrs. E. N. (5435.) The mother was a 27-year-old, Italian, para iv. Her first child, born in 1931, had a normal delivery and was living and well at the time of this pregnancy. Her past and family histories were noncontributory. She had a functional systolic murmur during the second pregnancy. Otherwise her antenatal course was entirely normal. Her blood test for syphilis at this time and on her first visit was negative.

She was delivered normally at term on Dec. 10, 1931, by low forceps. The child was a male and weighed 3,090 gm. The infant was covered with golden yellow vernix. It developed a deep jaundice during the first day of life. The heart was not enlarged but the liver and spleen were easily palpable. Blood studies showed 3.1 million red blood cells, 85 per cent hemoglobin, and 40,900 nucleated cells. There were 17.5 per cent of the red cells reticulated and 21.0 were nucleated. The bleeding and clotting time was normal. The patient was given a 60 c.c. transfusion. During the stay in the hospital it received five additional transfusions, and some intramuscular liver. The jaundice deepened and on December 29, it reached an icteric index of 325. The red count was 4.12 million eight days after birth. From this point on there was a fall on two occasions to 2.47 and 2.61 million, respectively. These periods of severe anemia were counteracted with transfusions. The nucleated red cells disappeared from the blood stream on the seventh day. The child was discharged on Feb. 1, 1932, with a slight persistent anemia. The icteric index had fallen to 75 at the time of discharge. The mother had a slightly febrile puerperium.

The placenta weighed 810 gm.

On Oct. 17, 1935, the patient was delivered normally, at another hospital, at term, of a normal appearing female child. The mother's prenatal course, according to her, was perfectly normal. The child became jaundiced during the first few hours of life. In spite of the mother's statement to the attending physician regarding a history of erythroblastosis, the child received no treatment. It died suddenly on the eighth day. The mother's postpartum course was uneventful.

On March 12, 1937, after a perfectly normal prenatal course, the mother was delivered normally of a 3,570 gm. male infant. Smear of the cord blood showed 17 per cent nucleated red blood cells. The baby became jaundiced after six hours. Blood studies at this time showed 5.4 million red cells, hemoglobin 100 per cent, nucleated cells 20,000, of which 2 per cent were red cells. The bleeding and clotting times were normal. The red cells had a slightly increased resistance to hypotonic saline. At the end of twenty-four hours, the spleen and liver were definitely enlarged. The jaundice deepened rapidly, and the skin became olive green in color. The patient was given a 50 c.c. transfusion on March 13, 1937. The next day there were no nucleated red blood cells. The jaundice disappeared on

March 17, 1937, and with this there was a progressive fall in the red count. When this reached 2.3 million, a 60 c.c. transfusion was given. The next day the red count was 2.18 million and a transfusion of 120 c.c. of blood was given. Following this transfusion there was a progressive rise in the red count to 4.75 million. The red count then fluctuated between 4.70 million and 4.03 million at discharge. The mother's postpartum course was uneventful.

The placenta weighed 540 gm.

The patient and child were living six weeks following discharge. The child was still quite anemic and was receiving treatment at the Boston City Hospital. The blood test for syphilis was not taken.

DISCUSSION: CONGENITAL HYDROPS

At first glance it would seem futile to derive statistical data from such a small series of cases. However, inasmuch as no similar series appears in the literature, it was felt that any data so derived would at least serve the purpose of indicating a trend.

Since 1930 there were 15 infants suffering from congenital hydrops born to 13 mothers in the Boston Lying-in Hospital. During the same period there were 30,299 deliveries. The incidence of congenital hydrops in this series is, therefore, approximately one in every 2,000 deliveries. Little pertinent information can be gained either on questioning the mothers or on examination of the records regarding the prenatal period. Toxemia in some degree occurred in 30 per cent of the cases or an increase of five times the incidence in the clinic. While this is of interest and has been noted by many of the German authors, it is felt that toxemia is rather an indication of a disturbed maternal metabolism and not an etiologic factor. Contrary to the prevailing opinion that the hydrops infants are heavier than normal, these infants average 6.6 gm. under the normal average given by (Riggs[7]). There is some error in this average due to failure to correct for prematurity in a few of the cases. This correction, however, is insignificant. The placentas average 1183.5 grams in weight and give a fetal placental ratio of 3 to 1 instead of the normal of 6 to 1. All the placentas present a typical pathologic picture. Sex played no factor in the series. Yellow vernix first described by DeLange and Artzenius[3] and later emphasized by Clifford and Hertig[2] as a diagnostic aid occurred only three times. It is seen so often in infants exhibiting fetal distress during the second stage of labor that it can be considered of negligible diagnostic importance. Icterus occurred in 30 per cent of the cases. This is one of the factors that helps to emphasize the close relationship between congenital hydrops and icterus gravis. The infant mortality in congenital hydrops is 100 per cent. The infants are either stillborn or live only a few minutes though one infant survived forty-eight hours. Autopsies were performed on all but two of the infants. Because of inadequate history and lack of post mortem examination, E. C. 13,627 (first erythroblastotic infant) did not conform to the criteria for diagnosis. However, the gross and microscopic picture of the placenta and the appearance of the disease in the subsequent child leaves little doubt as to the validity of the diagnosis. The autopsy findings were consistent throughout. All but one infant showed an increase in the fluids of the body cavities.

The heart, liver, and spleen were enlarged and extramedullary erythropoiesis was found in the liver and spleen without exception and frequently in other organs.

There are 11 females in which the disease was present first in the hydrops variety. The average maternal age is 31.6 years and the average parity is 5.2. This confirms the opinion that erythroblastosis is a disease of the middle or late child-bearing period and occurs only with the greatest infrequency in primiparas. This disease occurred in consecutive siblings in 2 of the 11 families listed, and showed, in the remainder, a definite tendency to be the final episode in the child-bearing histories of these mothers. Before the occurrence of erythroblastosis in these families there were 31 normal infants and 9 stillbirths. Following the birth of the erythroblastotic infant there were three normal children, three stillbirths, three infants with congenital hydrops and none with icterus gravis. In this group, therefore, the chance of having a second infant suffering from congenital hydrops is 50 per cent.

DISCUSSION: ICTERUS GRAVIS

There were 20 infants with icterus gravis born to 19 mothers during the period under consideration. The incidence is thus approximately one in 1,500 deliveries. The infants in this group were normal in weight and showed approximately equal sex distribution. Only a few of the placentas were saved for examination, but these showed a normal gross appearance and were of normal weight. It was only on microscopic examination that changes consistent with the diagnosis of erythroblastosis could be made out. The presence of yellow vernix was again of no diagnostic importance. However, anemia was present to some degree in 80 per cent of the infants. In most instances the anemia appeared late, after the disappearance of the jaundice and the circulating nucleated red cells. It is this fact and the failure to find any cases which satisfy the original criteria for the diagnosis of congenital anemia which lead, inevitably, to the conclusion that the so-called congenital anemia of erythroblastosis is not an entity but a sequel to icterus gravis. That the jaundice and increase in circulating nucleated red cells may be a very transient condition is well demonstrated in some of these infants. The infant mortality in this group was 53.8 per cent. It is evident that those infants who died were either not transfused or the transfusions were inadequate and were given too late. The entire group showed enlargement of the liver and spleen and occasionally the heart. This was also evident in the 6 post mortem examinations. Extramedullary erythropoiesis was present as in the previous group but to a less marked degree. The average age of the mothers is 30.1 years and the average parity 3.4. There was one primipara in this group. There were 44 normal infants and 6 stillbirths prior to the birth of the icteric infant. Following this there were 3 normal infants, 3 stillbirths, 1 child with congenital hydrops, and 12 with icterus gravis. The disease showed a familiar incidence in seven of the twenty

families considered. The chance of a subsequent infant suffering from erythroblastosis in this group is 80.3 per cent.

Because of the familial characteristic of the disease one family in each group was carefully investigated for 4 generations. There is no evidence that the disease has any congenital characteristics.

The similarity of the placentas of infants suffering from congenital hydrops to those described as occurring in infants with congenital syphilis led to a careful investigation of this aspect. The blood tests of all the mothers were negative either at the time of delivery, or at the follow up visit, during this investigation, or both. One mother, A. G., had a positive blood test at follow up visit but she showed no evidence of syphilis at the time of the birth of her child. At post mortem examination of the infants in the hydrops group the livers were stained according to the Levaditi method but no spirochetes were found.

CONCLUSIONS

1. Fifteen infants suffering from congenital hydrops and twenty suffering from icterus gravis are presented.

2. This represents an incidence of 1 in 2,000 deliveries in the first group and 1 in 1,500 deliveries in the second.

3. The infant mortality is 100 per cent in the first group and 50.3 per cent in the second.

4. The importance of the early diagnosis of icterus gravis and of early and adequate transfusion is emphasized.

5. Early diagnosis can only be accomplished with accuracy by careful placental studies and examination of the cord and infant blood in all suspected cases.

6. The incidence of recurrence of the disease in subsequent infants in the same family is 50 per cent in the first group and 80.3 per cent in the second.

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Schleyer, E.: New Symptom for Differentiation of Inflammatory and Noninflammatory Genital Tumors. Zentralbl. f. Gynäk. **61:** 1176, 1937.

Schleyer describes the value of rectoscopic examination in differentiation of inflammatory and noninflammatory genital tumors. He found that, if rectoscopy reveals proctosigmoiditis or sigmoiditis, the tumor of the genital adnexa generally is inflammatory, whereas normal mucosa in the sigmoid indicates a noninflammatory genital tumor.

J. P. GREENHILL.

PUERPERAL GANGRENE OF THE EXTREMITIES

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FORTUNATELY, post-partal and post-abortal gangrene of the extremities, with its very serious prognosis, is an extremely infrequent complication. In 1932, McNally collected 99 cases from the literature. To this series he added a case of his own, gangrene following a cesarean section. He reviewed the entire group, finding 72 cases of post-partal gangrene of the lower extremities, 12 cases of post-abortal gangrene of the lower extremities, 11 cases of post-partal gangrene of the upper extremities, 1 case of post-abortal gangrene of the upper extremities, and 4 instances in which gangrene occurred during pregnancy. Unquestionably, several of the cases included in the series are of doubtful authenticity, since it includes women who developed gangrene more than one month after labor, patients who had received ergot or one of its derivatives, and likewise, women in whom other basic maladies such as Raynaud's disease or toxemic states, such as eclampsia, existed.

Subsequent to McNally's report, Cutchin's case is the only one published in English. In 1934 he reported a multipara who had received 4 drams of ergot over a period of two days because of continuous and severe bleeding. Dry gangrene of both legs was definitely apparent by the twelfth day, at which time she died of pneumonia. In this case too, the significance of the ergot ingested must be evaluated.

The following case is of particular interest because of the minimal indications of infection preceding the onset of the gangrene, and because no other factors such as ergotism, excessive hemorrhage, or coincidental diseases need be considered.

L. M., a twenty-year-old white woman, married sixteen months, gravida i and para i, was admitted to City Hospital on Jan. 2, 1935, with the history of having been delivered at home with forceps on Dec. 17, 1934. Subsequent to delivery, there occurred a profuse, foul vaginal discharge. There were neither chills nor fever. She remained in bed after her delivery until she sought admission to the hospital because of pain and tenderness in her left leg.

Examination showed her general condition to be excellent. She was moderately obese. Tenderness and spasm were elicited in both lower abdominal quadrants. The uterus could be palpated 3 cm. above the symphysis. Exquisite tenderness of the left calf with glistening tenseness of the skin was noted. There was no evidence of venous pathology. The left foot was normal.

Two days after admission, the tenderness and swelling of the left calf had increased markedly and saphenous vein tenderness was evident. At this time, her temperature was 101° F. By January 5, the patient appeared quite ill, and had severe pain in both lower extremities. There was marked edema of both thighs, legs, and feet. Both feet were cool and livid. At this time, her temperature had dropped to normal levels.

On January 7, bleb formation was noted on the left leg, suggesting a burn. One week later, a large bleb on her right foot was aspirated, yielding 20 c.c. of straw-colored fluid which cultured negatively. On January 17, dry gangrene of the distal parts of the soles of the feet and the toes was definite. Both lower extremities were tensely swollen, although there was no pitting edema at any time. The tenderness gradually grew less. On this same date, the picture was complicated by infarction of the right lung base. Respiratory symptoms and elevated temperature were evident until January 29. On January 30, superficial gangrene of the left ankle was noted. At this time morphine gave very little relief of pain.

Disproportion between the temperature (98.4° F.) and the pulse (130) was first noted on February 13. At about this time, the lines of demarcation were gradually

deepening to the bone. On February 18, the right foot was amputated through the line of demarcation (through the tibio-astragaloid joint). On March 1, the left foot was amputated through the line of demarcation (including the lower two inches of the tibia and fibula). Up to March 15, the patient was more comfortable, and the stumps remained clean. During this period, opiates afforded relief. On March 20, she developed a large decubitus ulcer of the back. From March 25 to 30, the patient was intermittently delirious. She was discharged, upon her insistence, in a slightly improved condition, on April 6, 1935. Several blood transfusions had been

Fig. 1.—Appearance of feet on Jan. 17, 1935, one month after delivery. Dry gangrene is bilaterally evident, and the lines of demarcation are beginning to appear.

given during her stay at the hospital and repeated blood cultures had been negative. During the first two months of hospitalization, her temperature curve had swung between 100° and 103° F. Later it remained lower.

She was readmitted on April 22, and on April 25 was transferred to Bellevue Hospital (Psychiatric Division) where she died of sepsis on May 10, 1935.

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Mayor, J. M.: The Inhibitory Action of Follicular Hormone on Milk Secretion in the Puerperium. Zentralbl. f. Gynäk. **60**: 2379, 1936.

Mayor describes the results of treatment of 47 women who had been delivered recently and in whom lactation was not to be established. The cases included deliveries at term, premature deliveries and abortions. A hormonal injection was made during the first twenty-four hours after delivery and then once daily, the injection being intramuscular in each case: 14 patients were given menformon and the rest progynon B oleosum.

The author concludes: (1) intramuscular injections of follicular hormone undoubtedly have an inhibitory effect on mammary secretion. (2) Daily doses of 200 to 10,000 mouse units of follicular hormone, six to eight days after each other, produce no clinically valuable result. (3) Doses of 250,000 mouse units of follicular hormone in one injection yield a valuable clinical result. (4) The exact boundaries of the indications for such treatment will have to be worked out after further experience. The author suggests the use of follicular hormone in all cases of dead fetus or abortion.

J. P. Greenhill.

TRUE KNOT OF UMBILICAL CORD CAUSING FETAL DEATH BEFORE LABOR

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S. M., a 29-year-old, para 3-0-0-3,* was admitted to the University Hospital at term and in labor. Her family history included the history of one sibling stillborn, and the patient herself was born with a congenital absence of the left arm below the elbow joint.

Her prenatal course also had been characterized by a slight elevation of blood pressure which, however, was easily controlled by diet and purgation. The past obstetric history was entirely normal.

Admission examination revealed a term pregnancy, R.O.A., but persistent efforts to locate the fetal heart were unsuccessful and, upon questioning the patient, it was learned that there had occurred a complete and abrupt cessation of fetal movements seventy-two hours prior to the onset of labor which was preceded by a period of unusual fetal activity lasting approximately twenty-minutes.

Her labor was of normal progression and rectal examinations throughout gave the impression of a boggy presenting part instead of the usual firm sensation of the fetal skull bones. After nine hours she was delivered spontaneously of a full-term dead male child weighing 7 pounds 2 ounces.

There was a true knot of the umbilical cord 45 cm. from the placenta and 17 cm. from the child. Circulation was completely obliterated and the cord between the knot and the baby was enlarged, spongy, friable and darkened to a brownish-gray hue. The fetus was macerated and the cranial bones were overlapping. An autopsy was unobtainable.

Her puerperium was complicated by a mild puerperal infection lasting two days. She responded readily to treatment and after eleven days of hospitalization was discharged in good condition.

COMMENT

This case is an exception to the popular belief that knots drawn tightly enough to cause fetal death occur only during labor. The sudden extreme fetal activity preceding complete absence of movements is significant and is sufficient to make the diagnosis where no other pathology can be found. If the knot is tightened only during labor, the cause of fetal death in utero is more likely to be attributed to some other cause until delivery is effected. It follows, therefore, that careful inspection of the cord should be a matter of routine in all cases of stillborn infants.

I wish to thank Dr. L. H. Douglass of the Department of Obstetrics for permission to use this case.

*The first figure represents the number of full-term children whether alive or stillborn; the second, the number of prematures; the third, the number of abortions (before the twenty-eighth week); and the fourth shows the number of living children.

GANGRENE OF THE EXTREMITIES IN PUERPERAL THROMBOPHLEBITIS

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THAT puerperal gangrene is of rare occurrence is attested by the small number of cases recorded; reports in the literature indicate 105 to April, 1937. Infection is the common etiologic factor, with arterial obstruction mentioned as the direct cause of gangrene in most of the reported cases.

As is well known extensive thrombosis may occur in thrombophlebitis, complicating the puerperium, and the tense swollen leg show no signs of venous congestion. It is believed that this swelling may be due largely to lymphatic obstruction. The femoral vein in man may be ligated with only evanescent venous congestion and ligation of the femoral vein in dogs is followed by no congestion whatever (Homans[1]). The absence of venous congestion is explained by the ease with which venous blood finds its way past an obstruction, there being abundant pathways for the establishment of collateral circulation. Despite these facts gangrene may result from venous obstruction, as demonstrated by the cases I wish to report.

During a period of eighteen months three cases of puerperal thrombophlebitis which developed gangrene were seen at the Lawrenceburg Hospital, two following full term delivery and one following abortion. These patients, so far as could be determined, had no preexisting cardiovascular disease or other disease which might predispose to gangrene. Ergot had been administered to each of them before admission to the hospital, but the symptoms and physical signs did not suggest ergot poisoning. Three amputations were done, with the usual clinical criteria for determining the level of amputation being observed. In one case there was a definite line of demarcation. Femoral pulsation was felt in each case and arterial patency at the site of amputation was demonstrated by allowing momentary spurting. Careful dissection of the amputated extremities revealed obstruction of all the veins; the arteries were grossly normal and no obstruction could be demonstrated.

CASE 1.—Mrs. D. S. B., aged forty-four, para viii. There was nothing remarkable in her previous obstetric history. She was delivered of a 10-pound infant on Nov. 13, 1931, at full term and without difficulty. The attending physician had not seen her before the onset of labor but found the temperature, blood pressure, and urine normal. The pulse at the time of delivery was 120 and was found to be rapid at subsequent observations during the puerperium, this being suggestive of thrombophlebitis. Otherwise the puerperium was not remarkable until fourteen days after delivery when she began to complain of severe pain in the right leg. After three days the leg became cyanotic, moderately swollen and cold from the knee down. On December 6 the leg was black and cold; the toes were dry and there was complete loss of sensation downward from the lower portion of the upper third of the leg.

Hospitalization had been refused prior to December 7. On admission the temperature was 100° F. and the blood pressure 100/70. The abdomen was greatly distended but not tender. Fluids were given intravenously and subcutaneously, and amputation was done at the junction of the middle and lower thirds of the thigh several hours after admission. She recovered after a stormy convalescence, complicated by paralytic ileus.

CASE 2.—Mrs. A. S., aged 38, para ix; previous obstetric history not remarkable. She was delivered at full term on Oct. 25, 1932, by a midwife after being in labor for forty-eight hours. The membranes ruptured shortly after the onset of labor. She was first seen by a physician five days after delivery when she was having chills, sweats, fever up to 105° F., and foul lochia. On November 5 she began to complain of severe pain in the left leg and the extremity became tender and swollen. The temperature range continued high. On November 9 splotchy discoloration was noted over the foot and lower leg. Within forty-eight hours the foot and lower third of the leg were cold, of bluish black color and sensation was lost. A

definite line of demarcation appeared and amputation was done in the middle third of the leg on November 14. Convalescence was smooth and she was able to leave the hospital Nov. 25, 1932.

CASE 3.—Mrs. S. L. M., aged 30, para iii, was admitted to the hospital April 24, 1933, complaining of fever, chills, loss of weight and strength. She complained also of pain in the fingers, left elbow and hip and right knee. The onset of illness was three months before admission, beginning with vaginal bleeding; shortly thereafter the vaginal discharge became foul and profuse. Abortion was denied but she admitted amenorrhea of two months before onset of present illness. She looked gravely ill. The temperature was 103° F., and the pulse 130. There was limitation of motion and tenderness of the left elbow and right knee; the knee was slightly swollen. There was a foul vaginal discharge; the uterus felt a third larger than normal and was fixed in moderate retrodisplacement. Pelvic tenderness was definite but not pronounced and no adnexal or parametrial masses were felt. The blood culture yielded a nonhemolytic streptococcus.

Treatment consisted of supportive measures together with repeated small blood transfusions. On May 3 the right knee became more painful and the swelling increased. Bluish red spots were noted over the foot May 5; this discoloration increased and extended up the leg, which became cold and cyanotic. By May 8 the leg was definitely gangrenous and the patient appeared in extremis; however, she improved slightly following transfusion and amputation was done in the middle third of the thigh May 9. Only temporary improvement followed operation, the patient dying May 28, 1933.

Examination of the amputated extremity showed thrombosis of all the veins; the arteries were grossly normal.

Postmortem Findings.—The uterus was approximately a fourth larger than normal and bound to the posterior pelvic wall by adhesions. In the uterine cavity was found a mass of tissue measuring 3 by 3 by 2 cm.; it was firmly adherent to the uterine wall and was grossly a piece of placental tissue. The pathologist reported, "Sections of this tissue showed many decidual cells and degenerated tissue together with inflammation." The common, external and internal iliac veins were filled with thrombi. Each femoral vein contained a semisolid purulent material. The left pampiniform plexus was thrombosed as was the inferior vena cava in its first two inches. The abdominal aorta, the common, external and internal iliac and femoral arteries were grossly normal.

Similar in many respects to the preceding cases, yet differing in that gangrene did not occur, was the case of Mrs. A. M., aged 24, para iv, who was seen during February, 1937. She had been delivered by a midwife eleven days earlier. She complained of severe pain in the right foot and leg. The foot and lower half of the leg were cold, cyanotic, tender, and swollen. The foot and toes could be moved; however, tactile sensation was lost over the lower third of the leg and the foot, and deep sensation of the toes was lost. Femoral and popliteal pulsations were felt and it was thought the dorsalis pedis could be felt to pulsate. The treatment was heat, elevation, and medication for the relief of pain. Recovery took place instead of the expected gangrene. In the foregoing cases coldness, cyanosis and loss of sensation had presaged loss of the extremity. It seems logical to presume that all the veins were not thrombosed in this case, enough being patent for the establishment of collateral circulation.

SUMMARY

1. Four cases of puerperal thrombophlebitis are presented, three of which developed gangrene.

2. While rare, gangrene of an extremity may occur from the venous obstruction of puerperal thrombophlebitis when the thrombosis is unusually extensive.

3. Venous thrombosis of the puerperium is on an infectious basis. Case 3 illustrates the danger of leaving a fragment of placenta in the uterine cavity, which can usually be safely removed at the time of delivery if the principles of asepsis are respected.

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LIPOMA OF THE UTERUS ASSOCIATED WITH CARCINOMA

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WHILE lipomas are common tumors and frequently met with in all portions of the body, even in such unusual sites as the kidney and central nervous system, they are exceedingly rare in the uterus. The rarity of this condition is emphasized by the paucity of reported cases and that with few exceptions,[1, 2] these are on single cases. Moreover the only case in the Anglo-American literature seems to be that of Lund[3] who mentions approximately 10 cases culled exclusively from the German literature. He notes that the first case reported was that of Bruning who described an intramural uterine lipoma in 1899, and in addition to his 10 cases we have found 7 others reported in the last two decades.[2, 4-7] True lipomas have been reported also in the broad ligament,[8] and Murray[9] reports one weighing 17 ounces in the paravaginal region. In the uterus they may exist in almost any portion such as a leiomyoma might, and it is possible that they might extend into the ligaments or vaginal mucosa.

These lipomas resemble both histologically and grossly those in other regions and vary in size from a few millimeters in diameter to such a size that they suggest a pregnancy. This latter phase may be taken almost literally since the large tumors, being extremely soft, have been likened to the gravid uterus. Any symptoms arising from these tumors would merely simulate those caused by fibroids, that is, they depend very largely upon the size and location of the tumor mass, and as polypoid ones have been reported it can readily be seen that they might cause cramping pains and bleeding in much the same manner as a pedunculated subendometrial fibroid might. In two instances there has been a sarcomatous change[3, 5] or more properly speaking, one of the lipomas was termed malignant, but to our knowledge the present case is the only one which has ever been reported in which the lipoma was associated intimately with an adenocarcinoma or other malignancy in the same site. Most of the writers agree that they are generally found in patients of advanced age, although this is somewhat shaken by Muschik's patient[6] who was fifty-six years old.

Etiologically most writers agree that they are late developments of embryonic rests, but Gebhart[3] described lipomatous areas in mixed tumors of the uterus, and Pollack[3] thought that possibly some of the omental fat might have gained access to the uterine wall through some wound in its substance. There has also been some mention of a myxomatous degeneration in a leiomyoma producing a structure similar to a lipoma, a hypothesis that seems unsound and unaccepted.

Histologically, the tumors are usually sharply demarcated from the myometrium, although not definitely encapsulated. Merkel[1] noted in his case that unstriped muscle fibers extended directly from the wall into the central portion of the tumor, although this is unusual as most of the tumor sections can be described as merely typical lipomatous tissue. Grossly they appear as if they can be shelled out from the surrounding muscle and are yellow and greasy, resembling in every way the normal adult fat.

This case is also of interest because of the multiple tumors and what is obviously a fifteen-year cure of a carcinoma of the breast with involvement of the axillary nodes. Walkoff noted in his case of uterine lipoma that a lipoma of the left kidney also existed.[3]

REPORT OF CASE

CASE 1.—(No. 22193.) Mrs. E. H., housewife, aged 65 years, entered the hospital June 26, 1937, for the purpose of having a hysterectomy and vaginal repair for a third degree prolapse associated with a rectocele, cystocele, and enterocele. She had complained of pain and perineal irritation for years and had used a pessary for twenty, much of the irritation apparently had been due to the long continued use of the pessary. There has been some tendency to nocturia.

The family history is essentially negative and she has always made a good recovery from past illnesses. In March, 1922, she noted a lump in the right breast which started to increase in size in October of the same year and in two months it doubled in size. On Dec. 8, 1922, a radical mastectomy was performed by Dr. Deaver at the Women's Medical College Hospital in Philadelphia. Dr. Mollie A. Geiss reports that the tumor was diagnosed as a medullary carcinoma of the breast with mucoid degeneration and secondary involvement of the axillary nodes. Following this operation the patient remained in good health except that the right arm has maintained a size of some three times the normal, due to the circulatory and lymphatic block which followed the mastectomy. This finding on physical examination as well as the aforementioned profound prolapse constituted the only important physical findings, with the exception of a soft systolic murmur in the aortic area. The procidentia was so marked that on removing the pessary, and then having the patient cough, almost the entire uterus protruded from the introitus. The patient was somewhat obese, the pulse was 100 per minute and the temperature 98.6° F. Blood pressure was 195/105 mm.

The laboratory examinations showed a leucocyte count of 18,500, 4,230,000 erythrocytes and 84 per cent hemoglobin. The differential count on the blood smear showed polymorphonuclear leucocytes 70 per cent (of which 25 per cent were of the transitional type), 24 per cent lymphocytes, 2 per cent monocytes, 2 per cent eosinophiles, and 2 per cent myelocytes. The Kahn test was negative. The urine contained a rare hyaline cast and 7 leucocytes and 2 erythrocytes per high power field; the specific gravity was 1.018, and there was a trace of albumin.

On June 28, 1937, under cyclopropane and avertin the enterocele was dissected out and repaired and a hysterectomy was done by one of us (R. L. M.). During the operation the uterus was found to contain pus, and a malignancy was suspected. The patient felt well following the surgery and steadily improved for ten days. At that time she began to have chills, a high fever (105° F.), and tenderness in the left lumbar region, the urine then became loaded with pus and urinary cultures showed both *Escherichia coli* and Streptococci; blood culture was negative. The patient again improved, but three weeks after the operation again began to lose ground and a nonprotein nitrogen determination on the blood on July 25 was 200 mg. On the next day the patient died.

Pathologic Report (A. A. H.).—The specimen consisted of a uterus which was enlarged three times its normal size and whose wall was soft and boggy. The cervix was attached and showed a transverse laceration. The cervix and the uterus were connected by a thin isthmus of tissue. There was an ulcerated patch near the internal os; part of the wall was soft but near the endometrial cavity it appeared very hard and firm with friable and feathery areas, from the gross appearance it could be seen that the indurated and ulcerative process had penetrated deeply into the wall. About 1 cm. above the internal os was an intramural yellow tumor which was the size and shape of a large cherry, it protruded or bulged above the surrounding myometrium which was only partially infiltrated with the indurated tumor in this area, and resembled both by touch and appearance ordinary adult fat. There were some small abscesses scattered in the invaded portions of the myometrium which measured a few millimeters in diameter. These were filled with white and gray pus.

Sections through the yellow tumor showed a typical adipose tissue structure which appeared quite sharply demarcated from the myometrium (see Fig. 1), some of the neighboring tissue showed small bits of the infiltrating tumor. This tumor in some areas showed a typical adenomatous structure and would be classified as an adenocarcinoma (Grade II), it possesses polypoid fronds as well which were sur-

faced by tall columnar cells. In other areas were masses and sheets of typical squamous epithelium with the irregular distribution through the muscle which characterized epithelial malignancies, many of these bits of acanthomatous tissue were in close apposition to the adenomatous portions of the malignancy, but there was a sharp division and no gradual gradation from one type of cell to another (see Fig. 3).

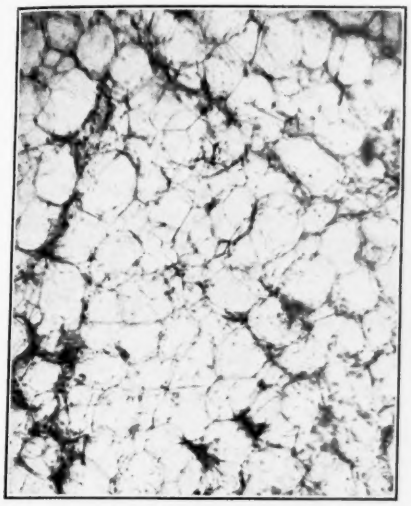

Fig. 1.

Fig. 2.

Fig. 1.—Section showing structure of the uterine lipoma. (×125.)

Fig. 2.—Cross-section of the uterus showing the lipoma. Note how it bulges above the surrounding myometrium. The cavity of the uterus is filled with the malignancy.

Fig. 3.

Fig. 4.

Fig. 3.—Section showing the adenoacanthoma, note the small islet of squamous cells near the center. (×125.)

Fig. 4.—Section of the myometrium showing a typical squamous cell area near the lipoma. (×125.)

Microscopic Diagnosis.—Adenocanthoma of the uterus associated with lipoma of the myometrium. Endometritis and abscess formation in the uterine wall secondary to the neoplasm.

Necropsy Report.—The heart was normal except for a very mild sclerosis of the coronaries and aorta. The lungs were adherent to the parietal pleura by firm adhesions throughout the upper lobes. The bases of both showed a decreased crepitus with increased consistency and on cross-section showed increased fluid and markedly decreased froth. The hilus nodes on both sides were calcified. The liver was yellowish brown in color and fat was detected in the scrapings. The spleen weighed 100 gm. and on cross-section showed an increase in connective tissue elements. The gastrointestinal tract appeared normal. The left kidney was enormously enlarged and occupied the greater part of the left side of the abdomen, and pus exuded through the fatty capsule, even before the kidney was removed. On cross-section it was made up of a number of large and small cysts which varied from pinpoint to walnut size; many of these were filled with pus and dirty fluid. The kidney measured 25 cm. in length and 15 cm. in diameter. The pelvis was filled with pus. The other kidney was somewhat smaller but the parenchyma had been replaced by cysts in the same manner, with the difference that these were filled with clear fluid, and there was no evidence of secondary infection. The bladder was somewhat injected and contained some purulent material. The old operative site showed a moderate injection and some minute abscesses. The left ureter traversed this area, but there was no apparent obstruction or lesion. There was no evidence of any metastases or metastatic glands, although some specimens were taken for sectional study. A very careful search was made in the right pectoral region and in the right axilla, but no evidence of recurrence of the old malignancy or enlarged or indurated axillary glands could be found.

Summary of Necropsy.—Bilateral polycystic kidney with a secondary inflammatory reaction in the left, resulting in a profound pyelonephritis. Terminal or hypostatic pneumonia of the lower lobes. Recent hysterectomy for procidentia and carcinoma of the uterus. There was no evidence of metastases in any area as a result of this malignancy or from the tumor of the breast which had been removed fifteen years previously.

DISCUSSION

This case is not only of interest because of the rarity of uterine lipomas, and because it is a proved case of a fifteen-year cure of carcinoma of the breast with axillary involvement, but also because it may, in a measure, explain the genesis of lipomas in this site as well as acanthoma. Ewing[10] covers the controversy concerning the origin of this tumor excellently in his book citing both the exponents of the theory of multicentric origin and those of metaplasia. He states that a variable histogenesis may occur in adenoacanthomas of the cervix but that those in the uterus may be on the basis of metaplasia in almost all instances and do not require original heterotopia of squamous cells. We suggest, that in this case, the evidence pointing to the development of discrete but intermingled masses of adipose, squamous, epithelial, and adenomatous tissue, must rest largely in the favor of multiple heterotopia. For while the transition or metaplastic change from adenomatous tissue to squamous cell structures has been long recognized and is frequently seen in the cecum and elsewhere, the idea, that by similar metaplasia we may develop lipomatous tissue from these epithelial structures, is somewhat remote. It may be even possible that a single heterotopic focus might have harbored all of these various tissue structures, but as stated in the pathologic microscopic examination these tissues, while being in close apposition, did in no wise tend to merge into the other and were distinct and separate tissue entities. While not impossible, we cannot entertain the idea of the breast malignancy being the primary cause of the uterine malignancy. Such a site, without other evidence of visceral involvement, would be beyond the realm of reason and further, it is a well known fact that such lesions, if secondary, would never display such a completely different type of malignancy, for while we have not seen the sections of the original tumor, the description that was forwarded, places it in a vastly different category. This is merely one of the numerous cases of multiple primary malignancy.

In passing, it is interesting to note that the hypertension is probably a result of the bilateral polycystic kidneys, an observation or finding which is not uncommon,[11] also that these cystic kidneys seem prone to be associated with various developmental errors in many cases and in this instance it is not unreasonable to regard the lipoma and even the two separate malignancies as developmental abnormalities.

SUMMARY

A case of lipoma of the uterus is presented which is associated with an adenoacanthoma of that organ. It is felt that the three various types of tissue tumors in the one organ may lend some support to the theory of the multicentric origin from various heterotopia. Lipomas of the uterus are rare findings, this being the second report in the English language. Incidentally, the case is a proved fifteen-year cure of cancer of the breast with axillary involvement.

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A MANIKIN FOR INDIVIDUAL STUDENT USE

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THE idea of utilizing a metal manikin for teaching the mechanisms of labor in vertex, brow, and face presentations was advanced by me[1] some time ago. The model which was described in this Journal has been sold at a price that made it possible for our school to install one in each of the six obstetric quiz rooms, the combined cost being no greater than the cost of one of the models that were formerly used. For use in my lectures to students and nurses, I have always carried one of these manikins in my car.

The efficiency of the device so impressed me that for many years I entertained the thought of producing a miniature that could be purchased for not more than the price of a textbook. This would enable the individual student to follow the mechanisms of labor in his own study.

Much disappointment was encountered, since I soon learned that pelves removed from newborn babies were no larger than watch charms. Thus it was evident that such could not be used for modeling. After much difficulty I was able to procure pelves from female children of various ages, only to meet with further disappointment. Pelves of the size that I desired were not completely ossified and consisted of too many parts. Also, in contour, they could not be regarded as miniatures of the normal adult female pelvis, especially as regards the shape of the inlet, as well as all other characteristics.

The original model of the pelvis here presented (Fig. 1) was made by hand and is an exact miniature of the manikin that I had originally described and which is now in use in many of the medical schools. This manikin, made of aluminum, is sup-

ported on a base, in such a manner that the inlet makes an angle of 42 degrees with the horizon, which I have found from my studies[2] to be the average normal pelvic inclination in the recumbent posture.

Accessory parts which interfere with visibility, are eliminated from this type of manikin.

The skull, likewise, is a miniature of the theoretically perfect fetal skull originally designed by me. In it are incorporated such features as: (1) Normal relationship between the biparietal and bitemporal diameters. (2) Visible sutures and fontanels.

Fig. 1.

(3) Prominent malar bones, which play an important part in the mechanism of brow presentation. (4) The skull is so shaped, that slight deflection causes the sinciput to descend below the level of the occiput—a feature that is essential for demonstrating the cause of backward rotation of the occiput, in occipitoposterior presentations. (5) The neck, which serves as a handle, is so attached as to create a two-arm lever, the longer arm extending toward the chin.

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Washington Medical Building

Herold and Effkeman: The Significance of Hormonal Disturbances in the Origin of Cystic Mastopathies and in Epithelial Metaplasias of the Cervix, Zentralbl. f. Gynäk. **61:** 1155, 1937.

Estrogenic hormones have a distinct influence on the development of tumors. This influence consists not of a disposition to stimulate tumors in general but only specific ones. However, such local growths arise only where there is a general tendency to tumor formation due either to hereditary factors, external factors or endocrine disturbances. The authors brought about changes in the cervix, uterus and breasts of animals by injections of estrogenic hormone. These changes resemble those seen clinically in human beings and considered to be precancerous.

J. P. Greenhill.

Department of Practical Problems in Obstetrics and Gynecology

CONDUCTED BY WILLIAM J. DIECKMANN, M.D.

TREATMENT OF PREMATURE SEPARATION OF THE PLACENTA

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PREMATURE separation of the normally implanted placenta is one of the most common as well as one of the most perilous complications of pregnancy. It occurs in about one-half to 1 per cent of all pregnancies and carries a maternal mortality of approximately 6 per cent and a fetal death rate of more than 60 per cent.

In this review of the available literature during the past five years, the period of gestation in the cases of premature separation reported was mentioned in 592 instances. The condition arose between the thirty-sixth week and full term in 334 or 56.4 per cent. In about 6 per cent complication developed just before the period of viability.

Reference was made to the etiology in 856 instances and pregnancy intoxication was accorded etiologically the predominant rôle in 611 or 71.9 per cent.

Maternal Mortality.—Premature separation of the placenta is not only responsible for a lamentably high maternal death rate, but for an especially high fetal death rate as well. In a study of 21 reports (Chart 1) comprising 2,319 cases, there were 145 maternal deaths, a mortality of 6.3 per cent.

In the collected case reports there is noted, however, a wide variation in the end-results, the maternal mortality ranging from nil in a series of 58 cases to 18.4 per cent in a group of 87 cases. These figures are not strictly comparable, because of the inclusion of varying periods of time. Obviously improved methods of diagnosis, as well as improved technical means of management, notably in recent years, have rendered a more favorable prognosis, especially for the mother.

The statistics of Baird as reported from the Glasgow Royal Maternity and Women's Hospital are especially impressive, because of the large number of cases cared for in a single institution. For the ten-year period 1925 to 1934 inclusive there were 1,160 cases, with a maternal mortality of 56 or 4.8 per cent. In this series of cases the results for the last five-year period did not show, however, improvement over the first five years, though it may be noted that the death rate for both was somewhat lower than the average.

Fetal Mortality.—Probably no complication of pregnancy is associated with a higher fetal mortality. In 1,012 cases the fetal death rate was 66.4 per cent. The lowest was 44.5 per cent. In a few small groups the fetal mortality reached 100 per cent.

TREATMENT

From a study of the various aspects of premature separation of the placenta, it becomes apparent that the therapeutic management of the condition must be almost equally as varied. No simple or specific therapeutic plan is applicable to all cases. Each case must be individualized and treated accordingly. Like gross obstetric hemorrhage in general, it is a major problem calling for mature judgment and wise guidance. Some one has poignantly stated that the fate of a patient suffering with grave obstetric bleeding is dependent largely on the first movement made by the attending physician.

Prevention.—In the practice of preventive medicine, no field is more fertile than obstetrics, and this is especially true with reference to the prevention of premature separation of the placenta.

Although the etiology of the complication is still somewhat obscure, the influence of toxemic disorders causatively, in a large percentage of cases, is almost universally accepted. It is, also, widely conceded that these conditions may largely be overcome by the assiduous practice of antenatal care. On this premise, it is reasonable to assume that measures directed antenatally toward the prevention of intoxication will diminish at the same time the incidence of placental separation.

Factors Influencing Treatment.—At the outset it must be borne in mind that the basic principles of management must be determined in each individual case. These are dependent on a large number of factors and may be considered under the following:

Condition of Patient.—In all instances it is incumbent, regardless of the type of treatment contemplated, either conservative or radical, that the age and parity of the patient, the presence or absence of toxemia, the condition of the cervix, the extent of bleeding with shock together with numerous other factors be seriously considered.

For example, in *elderly primigravidae,* especially in those cases associated with disproportion, it is clear that an expectant or conservative plan of therapy, delivery through the vaginal route, could by no means be considered favorably.

Parity must be considered equally, because it is well known that the death rate in multiparous is much greater than it is in primiparous patients, notwithstanding the observation that many more cases occur in multiparae than in primiparae. In Baird's series of 56 fatal cases, for instance, it was noted that 30 of the patients had 7 or more children, often in rapid succession.

The presence or absence of profound toxemia, particularly eclampsia, must always be seriously weighed before deciding on a definite plan of management. Patients with grave toxemia, notably the eclamptic patients, are poor subjects for major abdominal delivery, especially cesarean section.

Condition of Patient on Admission.—Because in many instances patients are admitted as emergencies, active treatment must be temporarily deferred and supportive measures instituted. Quiet and rest may be

afforded by the administration of morphine and blood loss restored by immediate blood transfusion. *In every case* this recourse should be adopted before, during, or immediately after delivery. As a temporary expedient, saline or glucose solution may be administered by hypodermoclysis or venoclysis. In numerous instances it has been definitely determined that the omission of blood transfusion in the management of late antenatal hemorrhage, arising especially from placenta previa and premature separation, was responsible for an increase in the death rate of almost 50 per cent. The transcendent value of blood transfusion may be appreciated when it is recalled that hemorrhage with shock is the chief cause of death in the great majority of cases.

Besides the foregoing, every means should be adopted to prevent further blood loss before, during, and after delivery, by either vaginal or uterine tamponade, observing every precaution, of course, to avoid contamination.

Next to hemorrhage with shock, septic infection ranks as the most common factor in mortality. Therefore every effort should be observed to avoid vaginal manipulation, except under the guidance of every possible aseptic safeguard. *It is a growing conviction that in all pregnant women after the thirty-sixth week of gestation the vaginal canal should, metaphorically speaking, be regarded as a hermetically sealed tube.*

Progress of Labor and Condition of Cervix.—The progress of labor, particularly with regard to the degree of cervical dilatation, is of fundamental importance in determining whether delivery should be accomplished by the vaginal or abdominal route.

With the cervix completely dilated and with the presenting part, vertex or breech, in the lower reaches of the vaginal canal, conservative forceps delivery or extraction may be practiced. With the cervical canal, on the other hand, uneffaced and only partially dilated or scarcely dilated at all, the far more preferable plan is delivery by low cesarean section. This in brief is the attitude most widely advocated and practiced in the treatment of premature separation, especially with relation to the cervix, today.

Type of Hemorrhage.—Another determining factor in the plan of management is the type of hemorrhage encountered.

In mild cases of "revealed" bleeding, provided local or cervical conditions are favorable, conservative measures may occasionally be instituted. Temporary control in cases falling in this category may be afforded by *aseptic* cervicovaginal tamponade combined with the application of a firmly fitting abdominal binder (Spanish windlass).

In "concealed" hemorrhage a more radical plan is imperatively indicated. In cases of this type abdominal delivery with generous blood transfusion should be adopted forthwith. Because it may progress with exceeding rapidity and without being readily recognized, concealed hemorrhage is most grave.

Condition of Placenta.—Obviously it would be of great advantage in deciding on a plan of treatment if one could determine the exact state of the placenta, or, in other words, the extent of its separation. This, naturally, is well nigh impossible.

If complete separation is suspected or recognized, immediate delivery, preferably by the abdominal route, is called for. The unfavorable condition, however, of the patient, often a complicating feature of the grave types of separation, may render prompt radical measures unpropitious or even impossible.

Condition of Uterus.—The state of the uterine wall is still another fundamental factor to be included in the principles of management of premature separation. Bleeding, mild or extensive, into the myometrium commonly denominated uteroplacental apoplexy or the uterus "Couvelaire" (named for Alexandra Couvelaire who first described the lesion) is always an extremely grave complication. With extensive invasion of the musculature, uterine contraction with retraction may utterly fail and favor thereby continued bleeding following delivery. Since the more common practice of cesarean delivery, the uterus "Couvelaire" has been found not an infrequent accompaniment of the severe cases of accidental hemorrhage, notably those of the concealed type. Extensive hemorrhagic invasion of the uterine wall increases the gravity of the complication, the fetus is invariably destroyed and the maternal mortality is definitely elevated.

While there still exists some uncertainty as regards the disposition of the uterus in uteroplacental apoplexy, it is generally conceded that hysterectomy should follow section in cases associated with extensive involvement of the uterine wall and particularly if the uterus fails to contract promptly.

The Fetus in Uteroplacental Apoplexy.—Generally speaking, relatively little consideration can be given the fetus in the management of this complication, because, first, of the grave prognosis for the mother, and second, because of the enormously high mortality for the fetus, irrespective of the type of treatment instituted. The present survey has indicated that in about one-half of the cases the fetus is premature and frequently nonviable. Moreover, in a large percentage of instances the fetus is dead before the onset of labor, most commonly as a result of the associated toxemia. In the severe cases of separation, owing to acute placental insufficiency, fetal death occurs before or shortly after the onset of labor. Unfortunately, the type of delivery most favorable for the fetus prognostically, namely, cesarean section, is undertaken generally in the severe cases in which the baby is already dead or the outlook for its survival extremely discouraging.

Active Treatment.—From what has been said thus far regarding therapy, it becomes at once apparent that no specific mode of management is applicable to all cases. Every case of premature separation, as a matter of emphasis, is an individual problem, calling for the most discriminating judgment in deciding on a therapeutic plan.

The complication should by no means ever be regarded as a *simple or ordinary problem and, hence, its solution does not come within the province of the ordinary man.* Immediate hospital care should be provided for all patients and all should receive the wise guidance and superior technical training of a skilled accoucheur.

The chief objectives in active treatment are two: first, the prompt delivery of the child with the detached placenta and, second, control of the bleeding. As a rule, with the extraction of the products of conception, further bleeding, of course, is effectively taken care of at the same time.

Combined with the foregoing, it is imperative in all cases that continued loss of blood be prevented by uterine tamponade following delivery from below and by hysterectomy following delivery from above, particularly in those cases associated with a hemorrhagic musculature and lack of uterine contractility.

In the mild case, very little or no interference at all is practiced locally, delivery being allowed to take place spontaneously or promptly brought to conclusion by forceps in vertex and extraction in breech presentations, provided, of course, the local or cervical condition is conducive to measures of this character.

In most of the papers studied in the present survey, the methods of delivery were classified as follows: Expectant, radical, surgical (cesarean section).

A comparison of the ultimate results following the adoption and practice of the foregoing methods disclosed that in most instances the mild cases were treated expectantly and more severe cases by some form of interference.

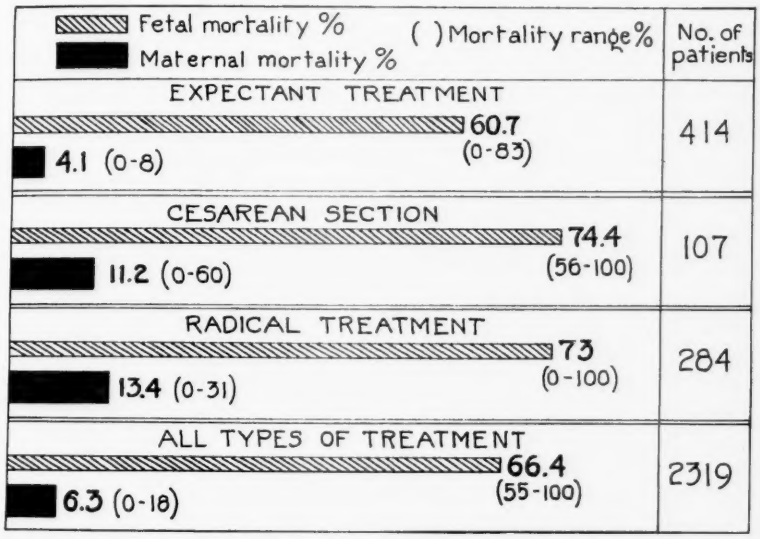

Chart 1.—Analysis of 2,319 cases of premature separation of the placenta, from representative clinics.

In many clinics, our study revealed that attempts were made to deliver almost all patients by a uniform or standard method of procedure.

The final results in the 805 patients studied in the present survey with regard to the type of treatment showed a maternal mortality of 8.4 per cent. These figures disclosed further facts of special interest: The mortality was lowest among those patients who were treated expectantly. In this group there were 414 cases with 16 deaths, a mortality of 4.1 per cent. The highest maternal death rate occurred in the radical group. Here there were recorded 284 patients with 38 deaths, a mortality of 13.4 per cent. Surgical methods yielded an intermediate mortality of 12 or a percentage of 11.2 in 107 patients.

A difference in the final outcome in the three different forms of management is quite impressive, but the comparison between the radical and surgical methods instituted is especially significant.

The patients treated by these two methods, radical and surgical, were those in whom the bleeding was of an acute type and in whom active interference was deemed imperative.

Radical treatment has been variously defined. It was observed in many of the reports studied that numerous measures were described including some of the simple obstetric maneuvers, as well as those of a more formidable character. For the sake of uniformity, we have incorporated in this division all manipulative procedures practiced vaginally.

The high mortality associated with the radical plan of therapy was due in great measure to the various types of vaginal manipulation and instrumentation including chiefly: a. Forceful dilatation of the cervix, b. Braxton-Hicks version, c. podalic version, d. extraction, e. embryotomy, f. the high application of forceps, and g. bagging.

To emphasize the part played in the mortality by methods of this nature, mention may be made of 6 deaths following 11 attempts at manual or instrumental cervical dilatation.

This method when contrasted with the simple expedient of puncturing the membranes indicates that it rarely should be considered in the management of premature separation. For example, in 35 cases of placental separation with only two deaths, simple rupture of the bag of waters was the only means employed.

In the reports emanating from the Irish Clinics, puncture of the membranes was noted as the most frequent form of obstetric intervention employed, with favorable results. Thus among 134 patients treated by conservative methods, the maternal mortality was only 8.4 per cent in contrast with an average mortality of 17.6 per cent in 153 patients treated conservatively in various other institutions.

Braxton-Hicks version and internal podalic version, with or without extraction, were employed in a small number of cases. Objection to these measures is based on the observation that not infrequently they add to the shock and favor infection.

Cervicovaginal tamponade is still recommended, but the use of the bag is gradually being abandoned, because in so many instances it proved ineffective and because of the risks of sepsis.

Of more than passing interest is the policy pursued in the large Irish maternities mentioned. In these institutions every effort is made to allow labor to progress along normal lines. Treatment is generally limited to the employment of routine supportive measures, especially the use of clysis, transfusions, morphia, and binders. Where intervention is practiced, it is along the simplest lines, using measures associated with the least amount of trauma and shock, as puncture of the membranes, cervicovaginal tamponade and, in severe cases, the delivery of a leg. It is notable that in the 278 cases reviewed from these institutions not a single abdominal delivery is recorded. The maternal mortality rates were well within the average combined percentage. However, it may be questioned whether the mortality may be further lowered without the use of radical procedures in the frankly severe cases.

The increasing employment of abdominal delivery in the treatment of premature separation was quite apparent in most of the articles studied. Most authors seem to agree that it is the method of choice in the following circumstances:

1. In cases associated with acute or violent bleeding.
2. In cases associated with extensive concealed hemorrhage.
3. In cases of complete separation.
4. In cases with the cervix long, uneffaced and undilated.

5. In cases arising in elderly primigravidae, especially in those with disproportion.

6. In cases displaying symptoms and signs of hemorrhagic infiltration of the myometrium.

7. In cases associated with tardy labor.

The end-results following routine cesarean delivery in the type of cases herewith enumerated were considerably more encouraging than the results following other methods of treatment in cases of a similar type. Nevertheless, it must be emphasized that the mortality rate following cesarean delivery in premature separation of the placenta (11.2 per cent) is more than twice as high as the accepted mortality of cesarean section in general.

The classical section was the most common type of operation performed. Low cesarean section figured prominently in the reports of many writers who are deeply convinced it should be used far more frequently in the treatment of this grave complication of pregnancy. This conviction is based on the observation that the maternal mortality is much lower following the cervical than the classical procedure.

Reference has been made previously to the disposition of the uterus in violent cases of premature separation. It is quite generally acknowledged that hysterectomy always should be performed, first, if the organ fails promptly to contract and, second, if the myometrium is infiltrated extensively with blood.

SUMMARIZATION

From the foregoing extensive survey of the available literature dealing with premature separation of the placenta for the five-year period, 1932 to 1936 inclusive, the following summarization may be made:

1. In a series of 249,331 deliveries, there were 2,319 cases of premature placental separation, an incidence of 0.93 per cent. It will be observed that the incidence is approximately 1 in 100 deliveries. In private practice it may be somewhat less and in hospital practice somewhat more than 1 per cent.

2. Premature separation of the placenta prognostically is one of the most perilous complications of pregnancy. It is associated with a maternal death rate of more than 6 per cent and a fetal mortality ranging from 45 to 100 per cent, and averaging about 70 per cent.

3. Since the cause of the condition is not definitely known together with the presence concomitantly of grave complicating conditions in many instances, pregnancy toxemia especially, it is obvious that no specific type of treatment is applicable to all cases.

4. The active treatment of premature separation is customarily classified into: Expectant, radical, surgical (cesarean section).

The expectant form of treatment employed in conjunction with supportive measures has proved most satisfactory in the management of the milder cases and is associated with the lowest maternal mortality rate. In the treatment of the severe cases, radical surgical treatment was very definitely superior.

5. The second, the radical plan, embracing various forms of obstetric maneuvers, as dilatation of the cervix, manual or instrumental, bagging, the high application of forceps, combined and podalic version, as well as

other means, is not ardently advocated nor practiced; first, because of the attendant dangers and, second, because of its far greater mortality.

6. In cases of premature separation arising in elderly primigravidae, especially if associated with cephalopelvic disproportion, the low cesarean section is accorded the treatment of choice.

7. The same recourse is regarded as the preferential plan in cases associated with an uneffaced and undilated cervical canal.

8. With the cervix completely effaced and dilated, combined with bleeding of a mild or moderate character, expectant measures, including puncture of the membranes, the application of a cervicovaginal tamponade together with a tight abdominal binder may be used.

9. In cases of an acute or violent character, accompanied by widespread hemorrhagic changes in the uterine wall and a lack of contractility, hysterectomy following delivery is favorably commended and practiced. On the other hand, the uterine body, provided the hemorrhagic infiltration is slight and with contractility present, may be retained.

10. It has been demonstrated most impressively that blood transfusion with hypodermoclysis or venoclysis before, during, and after delivery, in addition to other restorative measures, must be regarded as indispensable agencies in the therapeutic regime of all cases of premature placental separation.

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Winterton, W. R.: Continuous Drip Transfusion in Gynecology and Obstetrics, J. Obst. & Gynaec. Brit. Emp. **44:** 510, 1937.

The total quantity of blood in the average adult is approximately 10 pints. The customary transfusion of a pint of blood can do no more than raise the hemoglobin of the recipient by 10 per cent. In a severe case of anemia, such as an exsanguinated case of fibroids, the total hemoglobin after transfusion may still be less than 30 per cent. Recognition of this fact is the basis of drip blood transfusion. The amount of blood to be given in drip blood transfusion should be sufficient to restore the hemoglobin to the neighborhood of 80 per cent. This idea, however, may necessitate in grave anemia transfusions not far short of a gallon.

The introduction of such amounts by ordinary methods would result in gross increase of the blood-volume causing cardiac failure consequent upon overloading of the circulation. To overcome this difficulty the slow drip method was evolved.

A rate of 40 drops per minute is equivalent to a pint in four hours, i.e. a rise of 10 per cent of hemoglobin in an adult. This rate should be regarded as the maximal permissible rate of administration to a nonbleeding patient who is to receive several pints. In a patient who is bleeding the hemoglobin should still be increased by 10 per cent over four hours.

These large transfusions obviously necessitate a number of donors for each case. Little difficulty in obtaining donors has been experienced since the adoption of the practice of putting the onus of responsibility firmly upon the relatives. All donors must be of the same group as the patient and as each other.

J. P. GREENHILL.

Society Transactions

OBSTETRICAL SOCIETY OF PHILADELPHIA

MEETING OF OCTOBER 7, 1937

The following papers and discussions were presented:

Uterine Bleeding With Virilism. Dr. Virginia G. Rheuby (by invitation). (For original article, see page 119.)

The Potential Bisexual Character of the Ovary. Drs. A. J. Ramsey and J. F. McCahey (by invitation). (For original article, see page 111.)

Virilism and Female Pseudohermaphroditism With Relation to the Bisexual Nature of the Ovary. Drs. J. F. McCahey and A. J. Ramsey (by invitation). (For original article, see page 104.)

NEW YORK OBSTETRICAL SOCIETY

MEETING OF OCTOBER 12, 1937

The following papers were presented:

The Female Pelvis as a Focus of Infection in Arthritis. Dr. David N. Barrows.

The Effect of Estrogenic Hormone Upon the Contractility of the Fallopian Tubes. Drs. Samuel H. Geist, U. J. Solomon, and M. E. Mintz. (For original article, see page 67.)

Thiele, George: Coccygodynia, J. A. M. A. **109:** 1271, 1937.

Coccygodynia was found to be accompanied by spasm of the levator ani and/or coccygeus muscles in 64 of 69 patients seen by 9 different observers.

Spasm of the piriformis muscle was found in 31 of 33 patients with pain in the supragluteal region or down the back of the thigh.

In a series of 80 patients treated by massage by 8 different proctologists 60 per cent were cured, 33.7 per cent were definitely improved and 6.3 per cent were unimproved.

On digital rectal examination, with the patient in the Sims position, spasm of the levator is easily detected by lateroposterior pressure. The piriformis muscle is felt with the tip of the finger just distal to the sacrospinous ligament. It is most easily felt on the right side when the patient is lying on the left side and vice versa.

In all cases a uniform technic of massage has been used. With full length insertion of the finger in the rectum, lateroposterior pressure will place its flexor surface horizontally across the surfaces of the levator ani and coccygeus muscles almost at a right angle to their fibers. These muscles are massaged in the long direction. Massage is begun lightly. If definite improvement does not result after the first four to six massages over a period of a week or ten days, orthopedic or other indicated consultation should be sought.

GROVER LIESE.

Department of Reviews and Abstracts

Conducted by Hugo Ehrenfest, M.D.

Selected Abstracts

Sterility

Caffier, P.: Studies on the Mode of Transportation of the Human Ovum, Zentralbl. f. Gynäk. **60:** 1873, 1936.

The author presents clinical and experimental evidence that following the injection of prolan given in a dose of 3,400 rat units there will be found at the tenth and eleventh days of the cycle, an immediate apposition of the fimbriated end of the Fallopian tube on the rupturing or ruptured Graafian follicle. He believes that by means of this injection a situation is created which closely corresponds to the physiological process.

On the basis of his observations the author concludes that when the follicle ruptures, or immediately before, the fimbriated end of the Fallopian tube covers the rupturing follicle so that at the instant of rupture the ovum and the follicular fluid are injected directly into the ostium abdominale of the tube.

The ovum is conveyed into the desired direction mainly by the muscular action of the pars isthmica of the tube and in this mechanism the fimbria ovarica plays probably the important role. It is readily seen that for proper functioning of this mechanism, free mobility of the Fallopian tube is essential and it is therefore important, in certain cases of sterility, not only to ascertain the patency of the tube but also to restore its free mobility.

Richard E. Somma.

Daniel, Nitescu, Soimaru, and Georgescu: Study of the Physiology of the Fallopian Tubes in Women, Rev. franç. de gynéc. et d'obst. **32:** 421, 1937.

For pregnancy to occur, it is necessary not only that the Fallopian tubes be permeable but also that they possess the power to contract in order to direct the ovum toward the uterine cavity.

They experimented with 25 human tubes removed at operation and found: that tubal contractions began at the ampulla and were directed toward the uterine end; that nicotine in small doses increased the tonicity of the tubes but in large doses suppressed the contractions and paralyzed the tubes. In the presence of nicotine, adrenalin no longer was able to excite transitory tubal activity. Small doses of pituitary had no effect but large doses diminish the tonicity and frequency of tubal contractions. Prolan sensitizes the tubes to the effect produced by estrin. Corpus luteum also reduces tubal tonicity.

J. P. Greenhill.

Te Groen, L. J.: Some Aspects of Sterility, South African M. J. **11:** 725, 1937.

A detailed history of the marital relationship is essential. Dyspareunia, whether primary or secondary, requires attention. Treatment must be directed at the cause of the lesion. The general investigation of a sterility case is followed by examination of the semen shortly after coitus. The frequency of sterility due to the husband varies between 20 and 60 per cent.

The conditions of hypermenorrhea and polymenorrhea play a part in sterility, as well as vitamin deficiency. Diagnostic curettage is a valuable therapy for sterility. Ovarian dysfunction and uterine displacement require treatment. Insufflation and lipiodol injection of the tubes are becoming routine procedures to determine patency of the tubes. Injection of hormones, x-ray irradiation of the hypophysis and ovaries have their indications, as well as artificial insemination with husband's or donor's semen.

F. L. ADAIR AND S. A. PEARL.

Gierhacke, E.: The Fertility Vitamin E, Klin. Wchnschr. **15:** 221, 1936.

Vitamin E which controls fertility has heretofore been neglected clinically. Its use therapeutically in England, Switzerland, and Denmark in both human and veterinarian medicine has led the author to conduct a series of experiments which he describes in detail. This experimental work convinces him that vitamin E is most essential for the completely efficient reproductive life of both humans and animals. He is convinced that the administration of vitamin E is essential in the treatment of habitual abortion, primary sterility in the female and also in sterility of the male when this latter is not neuropathic in origin. The future, therefore, holds a rational form of therapy that should prove highly successful in these types of reproductive disorders.

RALPH A. REIS.

Albrecht, B.: Periodic Fertility and Sterility, Arch. f. Gynäk. **161:** 23, 1936.

There is an orderly and regular cycle of fertility and sterility in woman which is controlled by the biologic processes. This results in definite "fertile" and "sterile" days. The fertile days are linked with ovulation and are therefore the twelfth to the sixteenth days preceding the next menstruation. Two to three days preceding the above-mentioned days must be included since this represents the duration of fertilibility of the sperms.

It is absolutely impossible to determine the relatively sterile days with mathematical accuracy because of the well-known irregularities and variations of the normal menstrual cycle. Ovulation frequently is early and just as frequently is delayed.

However, the author believes that many of the sterile couples under treatment can be helped by an accurate determination of the fertile period and by careful instruction as to the optimum time for fruitful coitus.

RALPH A. REIS.

Guthmann, H., and Vetter, H.: The Question of Temporary, Physiologic Sterility Among Women, Monatschr. f. Geburtsh. u. Gynäk. **104:** 129, 1937.

The authors investigated the relationship of the time of conception to the menstrual period in 146 carefully controlled cases. They found a definite accumulation of pregnancies at a particular time in the cycle but nevertheless there was a wide spacing of conception in the menstrual cycle. Pregnancy was possible not only in the midinterval period but also just before and shortly after the bleedings. The authors insist that the use of the so-called safe period is not a substitute for operative or radiologic sterilization in cases where sterilization is indicated for medical or eugenic reasons.

J. P. GREENHILL.

Emge, Ludwig A.: Is the So-Called "Safe Period" Trustworthy? Western J. Surg. **44:** 28, 1936.

A careful analytical study of all available data leads the writer to various conclusions, among them the following: There no longer can be any doubt that the period of conception includes minimal and maximal possibilities in each menstrual cycle, regardless of the divergence of opinions regarding the exact position of the

maximal point of fertility. We may presume that like in animals also in the human female some variability occurs in this position. As far as we know, gametes of the human species retain the factor of fertility only for a short period. Therefore, fertilization must follow in close sequence to cohabitation, assuming that only one ovum is produced in each cycle. Absolutely regular cycles are uncommon. Unexpected irregularities in menstruation can occur at any time. Hence, one must doubt the infallibility of the Ogino-Knaus theory of a "safe period," even if applied only in the strictest sense of limiting it to known cycles of minor variabilities.

Popularization of the thought of a safe period is prone to bring much unhappiness. The problem still is subject to debate and the laity should be informed that the matter is not settled.

HUGO EHRENFEST.

Béclère, C., and Francois, E.: Chronic Genital Infection in the Etiology of Persistent Sterility in the Female, Bull. Soc. d'obst. et de gynéc. **26**: 709, 1937.

Of 110 cases of sterility of the female studied by the authors, only 11 of the patients became pregnant. In almost half of the remaining 99 women, both tubes were completely closed. In more than three-fourths of them the tubal obstruction was due to chronic genital infections and in nearly two-thirds of these cases the causative organism was the gonococcus.

In one-fourth of all the sterile women the tubes were patent but the lumen was markedly constricted. In over three-fourths of these cases, the cause of this was a chronic pelvic infection but the gonococcus was responsible for only one-third of these infections.

In the remaining one-fourth of the authors' sterile women, the tubes were normally patent. However, frequently the permeability could not be determined at the time of examination or only after using very high pressures. Likewise in these cases chronic pelvic infection was found in three-fourths of them. A positive gonococcus reaction was obtained in one-half of these cases.

J. P. GREENHILL.

Graf, A.: The Fertility of Women After Amputation and Paquelin Treatment of the Cervix Performed for Erosions and Elongation of the Cervix, Monatschr. f. Geburtsh. u. Gynäk. **105**: 272, 1937.

Many authors have reported that miscarriages and sterility follow amputation of the cervix. Therefore Graf undertook to follow up all the patients who had cervical amputations at the Düsseldorf Woman's Clinic since 1928. He found 21 such cases. Only 4 of these women subsequently became pregnant while the other seventeen remained sterile in spite of good cosmetic results. In the same period of time 25 women were treated with the Paquelin cautery and none of these subsequently became pregnant.

The author explains the sterility which follows amputation of the cervix as follows: Normally the cervical secretion, which is alkaline, bathes the upper part of the vagina. This produces a favorable medium for spermatozoa. When the cervix is removed, this alkaline secretion is missing and the sperm cells come to rest in an unfavorable acid medium. Furthermore, the spermatozoa have difficulty getting into the uterine cavity because there is no cervix dipping down into the posterior vaginal fornix.

J. P. GREENHILL.

Weiser, Frances J.: The Relationship of Contraception to Sterility, J. Contraception, **2**: 78, 1937.

Medical writers occasionally have stated that the prolonged use of any preventive measure may produce relative sterility, i.e., may delay conception. Weiser investigated this problem from clinical records and now presents the following findings: The contraceptive prescribed at the clinic had been employed by these women for from three to forty-two months before pregnancy was decided upon.

More than 50 per cent had used the method for one year or longer. After discontinuation of contraception impregnation occurred in 50 per cent within the first month, and in a total of 65 per cent within three months. Of the women using protection for a year or more better than 55 per cent conceived within three months after planning a pregnancy.

Contraceptive measures as prescribed by this clinic apparently do not play any role in the causation of sterility or in the time required for conception.

HUGO EHRENFEST.

Huhner, M.: The Huhner Test in the Diagnosis of Sterility Due to Necrospermia, Japanese J. Obst. & Gynec. **19**: 508, 1936.

The up-to-date gynecologist very wisely refuses to treat a woman for sterility until satisfied that the husband is not at fault. He therefore first examines several condom specimens (one is not enough) and if he persistently finds only dead spermatozoa, he instructs the patient to have her husband examined by a urologist and treated for this condition.

Many years ago Huhner made a series of experiments which showed that virulent gonococci do not interfere with the vitality of spermatozoa and are not therefore a cause of necrospermia. Whenever gonorrhea causes sterility, it is due to the pathologic changes brought about in either sex by the gonorrheal inflammation (occlusion of the vas in the male or closure of the Fallopian tubes in the female).

Huhner for many years called attention to an artificial necrospermia which is not uncommon. He refers to those cases in which the patient, fearing that the condom specimen would become cold before it reaches the doctor, either puts the condom in a jar of supposedly warm water or else places the condom wrapped in a towel underneath a hot water bag or on a hot radiator. In these cases the heat is too great and all the spermatozoa are killed at once. For this reason Huhner for years advised his patients not to use any heat at all in connection with the condom specimen. At times also the powder, which manufacturers place into condoms to help their easy application, has a detrimental effect on the vitality of the spermatozoa.

Huhner has seen quite a few cases in which he has examined many condom specimens with all the precautions previously mentioned, and in some cases as early as twenty minutes after coitus, and always found only dead spermatozoa in the condom and yet a post-coital examination (Huhner Test) revealed very many, very lively normal spermatozoa in the wife's vagina. In some of these cases the spermatozoa removed from the female genitals after coitus remained alive for several hours under the microscope while in the condom specimen they were found dead within twenty minutes.

J. P. GREENHILL.

Ranson, R. M.: Rubber and Sperm-Survival, Lancet **1**: 1400, 1937.

A study was undertaken to determine the spermicidal potency of rubber sheaths. The specimens were collected in sheaths, immediately transferred to glass tubes and transported to the laboratory. There 0.5 cm. of semen was transferred to the sheaths of the tests and kept at 37° C. In control tubes the sperm remained at full activity for five hours. In highly spermicidal sheaths all sperms were dead in three-quarters of an hour. The most spermicidal sheaths appear to be latex rubber and the least those made of molded rubber.

H. CLOSE HESSELTINE.

Williams, W. W.: Examination of Suspected Semen Stains for Spermatozoa, J. Lab. & Clin. Med. **22**: 1173, 1937.

Spermatozoa, when dried on clothing or elsewhere, maintain their morphologic characteristics and staining properties over long periods of time. This fact is of medicolegal importance. The following technique has been found useful in demonstrating spermatozoa: A small piece of the soiled cloth is treated with two drops of saline solution and with a blunt edge of a scalpel the surface is scraped upon

a slide. After drying, the film is fixed with heat, and stained with a modified Wollschwartz solution, washed with water and counterstained with Loeffler's methylene blue. This stain imparts a dull grayish color to every thing except the heads of the spermatozoa; the latter stand out as bright golden or yellowish spots in this gray background. The stain is exceptionally selective for spermatozoa; the spermatozoon heads maintain their morphologic characteristics indefinitely. The stain further serves to identify spermatozoa of different species as well as of different individuals of the same species.

W. B. SERBIN.

Douay: Hysterosalpingography and Its Dangers, Bull. Soc. d'obst. et de gynéc. **25:** 514, 1936.

Since 1927 Douay and his associates have made 1,409 hysterosalpingograms. The fact cannot be denied that the procedure is dangerous. Furthermore, in his opinion, the interpretation of the films is more difficult than the operation itself. Even after years of experience, mistakes can be made in interpreting the x-ray plates. By means of a special apparatus the author has obtained good results. He mentions a number of abnormal occurrences especially injection of lipiodol into the peritubal tissue and into the veins of the uterus, and from these into the large veins. Serious complications may arise when lipiodol is employed in the presence of an open hydrosalpinx because occasionally the retained substance transforms the hydrosalpinx into a pyosalpinx. In four of the author's cases infection resulted in such cases. In one patient, an abscess was opened by colpotomy and in two other patients hysterectomies had to be performed.

Because of the risks of lipiodol the author first employs the Rubin test in cases of sterility.

J. P. GREENHILL.

Mocquot, Palmer, Lejeune, and Razi: Hysterographs With Lipiodol Controlled Manometrically With Low Pressures, Bull. Soc. d'obst. et de gynéc. **25:** 519, 1936.

The authors found that after injection of lipiodol into the uterus, contractions of the latter were useful but not indispensable for the propulsion of lipiodol into the tubes. If a pressure of 5 to 7 cm. Hg was used, lipiodol entered the tubes but if only 4 cm. of pressure was used, the oil remained in the uterine cavity. This is very important to know because when lipiodol is injected into the uterus in cases of carcinoma it is most important to avoid getting lipiodol into the tubes.

J. P. GREENHILL.

Margraf, B.: Tubal Insufflation and Salpingography, Arch. f. Gynäk. **161:** 135, 1936.

The author reports a series of 160 women in whom tubal insufflation, salpingography or both were done for sterility. In 122, the tubes were patent but only 22 became pregnant subsequently. One of these and four of those with tubes closed developed tubal pregnancies and 17 carried the pregnancy to term. Tubal insufflation with or without hysterosalpingography probably has definite therapeutic as well as diagnostic value in the treatment of sterility. The author calls attention to the high incidence of tubal pregnancy following these procedures.

RALPH A. REIS.

Brault, P., and Tizon, A.: Hysterosalpingography and Sterility, Bull. Soc. d'obst. et de gynéc. **26:** 262, 1937.

The authors report their results in 50 cases of hysterosalpingography performed in sterile women. Sixteen of these women (32 per cent) became pregnant. Of these 16 women, 13 had living babies, 2 had abortions and 2 had ectopic pregnancies. In the patients who had the ectopic pregnancies, the tubes appeared abnormal on the x-ray

plates and the authors had given these patients an unfavorable prognosis. The authors did not observe any bad effects from the hysterosalpingography.

J. P. GREENHILL.

Bonnet, L.: Kymographic Tubal Insufflation, Bull. Soc. d'obst. et de gynéc. **25:** 666, 1936.

The author has employed tubal insufflation since 1922. A few months ago he reported his results with this procedure and reported an 18.4 per cent incidence of pregnancy following its use. He has given up the ordinary method of carrying out a tubal patency test and now employs the kymographic method recommended by Rubin.

By means of a kymographic record one can differentiate between a tube which is normally permeable, which is impermeable, which is undergoing spasm or actually stenosed, that is a tube whose lumen is more or less constricted due either to external or internal causes.

During the last few years Rubin has demonstrated that there exists a relationship of cause and effect between the hormonal function of the ovary and the peristaltic movements of the Fallopian tubes. Hence analysis of the kymographic records, in certain cases, will yield information about the condition of the ovaries. At the time of ovulation on the tenth to sixteenth day, the required pressure of the gas is at a maximum as is also the number and amplitude of the tubal oscillations. On the other hand, in cases of amenorrhea and at the menopause, gas goes through the tubes at a reduced pressure and the amplitude and number of oscillations are reduced.

Kymographic insufflation is superior to hysterosalpingography.

J. P. GREENHILL.

Béclère, C.: Sterility Due to Incomplete Tubal Obstruction and Its Treatment by Diathermy, Bull. Soc. d'obst. et de gynéc. **26:** 453, 1937.

Since 1929 Béclère has found tubal closure in 55 per cent of the cases he has studied but the closure was incomplete in about 30 per cent of the cases. He found that after salpingography, pregnancies occurred four times more frequently in the women who had bilateral permeable tubes than among those with abnormal or diminished tubal patency.

In most cases of partial tubal closure, the cause is an attenuated chronic infection. To overcome such infections the author advocates prolonged diathermy treatment in association with vaccinotherapy. If the cervix is infected, electrocoagulation should also be employed after diathermy. Of great importance is treatment of the husband as well as the wife, otherwise reinfection may take place. Therefore, the best chances for a pregnancy are obtained by treating both mates.

J. P. GREENHILL.

Dalsace, J., and Wechsler, R. B.: Short Waves and Diathermy in the Treatment of Female Sterility, Bull. Soc. d'obst. et de gynéc. **26:** 391, 1937.

In the opinion of the authors, diathermy and short wave therapy give indisputable results in the treatment of sterility. Their action on the source of infection permits to overcome tubal obstruction. The shorter the period of sterility the better the results. Hence, every attack of salpingitis should be treated as early as possible, as soon as the acute symptoms have subsided. Not only are excellent results obtained in cases of sterility by means of diathermy and short wave therapy but also these forms of treatment are followed by pregnancies in women who have dysmenorrhea, and those who have uterine and ovarian hypoplasia.

J. P. GREENHILL.

Kuestner, H.: Results of Salpingostomy, Arch. f. Gynäk. **161:** 135, 1936.

The author reports the collected statistics from 37 clinics. This group includes 93 operations of reimplantation of the tube into the uterus. In the majority of cases, this was carried out on both tubes. There was one death from embolism. Ten patients complained of severe dysmenorrhea following the operation. Postoperative tubal patency tests on 50 of these patients showed at least one patent tube in twenty. While in the remaining 30 patients both tubes were found closed. Ten patients had subsequent pregnancies; of these 2 miscarried and 8 were delivered of full-term babies. A patient has, therefore, only a 10 per cent chance of achieving a pregnancy as a result of this type of operation.

RALPH A. REIS.

Green-Armytage, V. B.: Tubo-Uterine Implantation for Sterility Followed by Full-Term Pregnancy, Brit. M. 2: 6, 1937.

A successful case is reported of the use of tubal implantation in the treatment of sterility in a patient who had previously been sterilized by tubal resection. A modified Bonney technique for tubal implantation is described. The author encourages the adoption of this procedure rather than salpingostomy. The technique is simple, and complete hemostasis is obtained by clamping the cervix and using a ring forceps on the infundibulo-pelvic ligaments.

This operation is useful whether the occlusion of the tube is at the fimbriated or at the cornual portion.

F. L. ADAIR AND S. A. PEARL.

Hartmann, K.: Tubal Changes Following Madlener Sterilization, Arch. f. Gynäk. **162:** 407, 1936.

Careful serial sections were carried out by the author on four sets of uterine tubes which were removed at varying intervals following sterilization by the Madlener method. Findings are described in detail, the most characteristic change being a complete hyalinization of the loop. In none of the tubes studied was the lumen patent nor could any fistulas be demonstrated. The author therefore believes that failure following the Madlener type of sterilization is not due to the method but rather to the faulty carrying out of the exact technique. Such failure is caused by insufficient crushing of the loop.

RALPH A. REIS.

Gerloff, Klaus: Advances in the Treatment of Sterility, Zentralbl. f. Gynäk. **60:** 2365, 1936.

Gerloff reports the results obtained in 102 women treated for sterility. No cases were included in which steriilty was due to severe hormonal disturbances. In 16 cases, treatment resulted in pregnancy which corresponds to 15 per cent of the total cases.

The author believes that better results would be obtained if the true cause of sterility could be determined in every case. In the majority of cases, however, sterility probably is due to multiple factors.

RICHARD E. SOMMA.

Van Tongeren, F. C.: Uterine Probing as a Simple Means of Treatment of Sterility in the Female, Arch. f. Gynäk. **161:** 143, 1936.

The author has been carrying out probing of the uterine cavity as a simple means of treating sterility in women for many years. He states that it is a harmless procedure when done under strict asepsis. The optimum time for using it is the tenth day of the menstrual cycle—which is just before ovulation.

This avoids injury to an early or unrecognized pregnancy. It should never be carried out in the presence of inflammatory disease or complete retrodisplacement of the uterus.

The results obtained in 150 patients in the Amsterdam clinic are reported: 47.5 per cent of women of the series became pregnant following probing; 33 per cent of women with primary sterility became pregnant, and 72 per cent of women with relative sterilities achieved pregnancy; 39 per cent of women became pregnant within six months, and 35 per cent of 115 who were sterile for more than three years became pregnant within six months.

RALPH A. REIS.

Items

Pacific Coast Society of Obstetrics and Gynecology

The next meeting of the Pacific Coast Society of Obstetrics and Gynecology will be held in Los Angeles, November 30 to December 3, 1938. Headquarters will be at the Ambassador Hotel.

Newly Elected Officers of Societies for the Current Year

NEW YORK OBSTETRICAL SOCIETY

President, Dr. Benjamin P. Watson; First Vice-President, Dr. William S. Smith; Second Vice-President, Dr. Thomas C. Peightal; Secretary, Dr. Henry T. Burns; Assistant Secretary, Dr. Ralph A. Hurd; Treasurer, Dr. William T. Kennedy.

PHILADELPHIA OBSTETRICAL SOCIETY

President, Dr. R. A. Kimbrough, Jr.; First Vice-President, Dr. Thomas B. Lee; Second Vice-President, Dr. G. A. Outerbridge; Secretary, Dr. R. W. Mohler; Treasurer, Dr. J. V. Ellson; Councillors, Dr. Norris W. Vaux, Dr. George A. Ulrich, Dr. George M. Laws, and Dr. Lewis C. Scheffey.

National Congress of Obstetrics and Gynecology

The first National Congress of Obstetrics and Gynecology will be held in Cleveland from September 11 to 15, 1939. The management is in the hands of the National Committee on Maternal Welfare, Inc., and the address of the same is 950 Rush Street, Chicago, Ill., where further information may be obtained. A tentative program is being developed which will soon be announced. There will be scientific sessions devoted to the discussion of various problems in the special domain of obstetrics and gynecology as well as in allied fields, including nursing, public health, social service, etc. A large exhibit hall will provide for both scientific and commercial exhibits.

Interested persons are urged to become members of the Congress, the fee for which is five dollars, and an active membership campaign is now under way in each state. The central office at 950 Rush Street, Chicago, Ill., will be glad to receive subscriptions. The general interest thus far manifested should assure a large attendance.

The personnel of the various committees and further news items will be published in subsequent issues of the JOURNAL.

American Board of Obstetrics and Gynecology

Candidates certified by the American Board of Obstetrics and Gynecology by examination, June 13 and 14, 1938, San Francisco, Calif.

ARTHUR WESLEY ALLUM, Glendale, Calif.
HAROLD CEDRIC ALWARD, Los Angeles, Calif.
EDMUND F. ANDERSON, San Francisco, Calif.
PHILIP H. ARNOT, San Francisco, Calif.
L. GRANT BALDWIN, Pasadena, Calif.
GRANT S. BEARDSLEY, Eugene, Ore.
LOIS HOLMES BROCK, San Francisco, Calif.
IRA BROWN, Chicago, Ill.
E. F. BRUNING, Santa Ana, Calif.
WILLIAM CARLISLE, Chicago, Ill.
WILLIAM J. CARRINGTON, Atlantic City, N. J.
PHILIPS JOHN CARTER, New Orleans, La.
J. ALSTON CLAPP, JR., Houston, Texas
C. J. COLLINS, Orlando, Florida
WILLIAM PAUL COOK, Los Angeles, Calif.
CHESTER L. COOLEY, San Francisco, Calif.
ROGER SIMMONS COUNTRYMAN, St. Paul, Minn.
DONALD ALEXANDER DALLAS, San Francisco, Calif.
LAURA DASEF, Akron, Ohio
BERNARD DAVIDOFF, Long Island City, N. Y.
DANIEL J. DAVIES, Cincinnati, Ohio
J. VERNON ELLSON, JR., Philadelphia, Pa.
CARL WILLIAMS EMMONS, Salem, Ore.
ROBERT HALDERMAN FAGAN, Los Angeles, Calif.
JOHN MARTIN FREIHEIT, Waterbury, Conn.
A. C. GARDNER FROST, Vancouver, B. C.
HENRY C. GERNAND, Los Angeles, Calif.
PETER GRAFFAGNINO, New Orleans, La.
HERVEY KING GRAHAM, San Diego, Calif.
CHARLES CLARKE HALL, Oakland, Calif.
FLORENCE WHITE HARK, Chicago, Ill.
JOSEPH MORRIS HARRIS, Los Angeles, Calif.
CAVINS DETER HART, San Francisco, Calif.
ROBERT J. HAWKINS, Chicago, Ill.
CHARLES T. HAYDEN, San Francisco, Calif.
GEORGE W. HEWITT, Los Angeles, Calif.
PAUL E. HOFFMANN, San Francisco, Calif.
MAURICE L. HORWITZ, Oakland, Calif.
CHARLES E. HUNT, Eugene, Ore.
G. WILSON HUNTER, Fargo, N. D.
GEORGE E. JUDD, Los Angeles, Calif.
GEORGE E. KLEEMAN, JR., Oakland, Calif.
HARVEY LEE KINCAID, Houston, Texas
FRANK E. KLIMAN, Los Angeles, Calif.
LEON KROHN, Los Angeles, Calif.
WOODBURN K. LAMB, Berkeley, Calif.
LEONARD A. LANG, Minneapolis, Minn.
DAVID LAZARUS, New York City, N. Y.
FLOYD JAMES LEE, Santa Monica, Calif.
ERNST LÖHNBERG, San Francisco, Calif.
JEROME P. LONG, JR., Memphis, Tenn.
WENDELL LONG, Oklahoma City, Okla.
A. M. MCCARTHY, Los Angeles, Calif.
A. M. MCCAUSLAND, Los Angeles, Calif.
FRANK L. MCPHAIL, Great Falls, Mont.
ALFRED L. MADDEN, Albany, N. Y.
ERIC M. MATSNER, New York, N. Y.
HERBERT L. MICHEL, Chicago, Ill.
LEE MONROE MILES, Albuquerque, New Mexico
DANIEL GREEN MORTON, San Francisco, Calif.
JAMES C. MUIR, San Jose, Calif.
MARY PETTIT, New York City, N. Y.
WILLIAM DAVIS PHILLIPS, New Orleans, La.
STIRLING GAINER PILLSBURY, Long Beach, Calif.
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PAUL R. ROLLINS, Seattle, Wash.
GLENN N. ROTTON, Seattle, Wash.
KARL L. SCHAUPP, San Francisco, Calif.
PHILIP F. SCHNEIDER, Evanston, Ill.
MARGARET SCHULZE, San Francisco, Calif.
FLOYD B. SHARP, Phoenix, Ariz.
FRED BAIRD SMITH, Houston, Texas
FRANCIS A. SNIDOW, El Paso, Texas
RAYMOND ROSCOE SQUIER, New York City, N. Y.
LELAND EARLE STILWELL, Hollywood, Calif.
JAMES JAY SWENDSON, St. Paul, Minn.
HOWARD CANNING TAYLOR, JR., New York City, N. Y.
CURTIS HARTMAN TYRONE, New Orleans, La.
HANS VON GELDERN, San Francisco, Calif.
VERNON L. WARD, Ogden, Utah.
HAROLD G. WATSON, San Francisco, Calif.
A. N. WEBB, Los Angeles, Calif.
PAUL W. WILLITS, Grand Rapids, Mich.
PAUL W. WINDER, Shreveport, La.
LEONARD WOODS, Oakland, Calif.

Fig. 1.—Gross-colored illustration of an ovary showing two recent ovulations. Note the hemorrhage covering the rupture site and a part of the surface of the ovary. A small amount of free blood was present in the peritoneal cavity. In addition to the ovulations present in this ovary, at least another freshly ruptured follicle was present in the ovary left in situ.

Unit Number 92689. Aged 28 years. Menstrual cycle, 24-day type. Endometrium, early proliferative. Day of cycle when hormone was administered, fourteenth. Time elapsed from the administration of hormone to removal of ovary, 38 hours. Amount of gonadotropic hormone injected, 50 units.

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